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THE CEREBROSPINAL FLUID OF PREMATURE INFANTS

WITH SPECIAL REFERENCE TO INTRACRANIAL HEMORRHAGE AND PIGMENTATION *

JEROME GLASER, M.D.

CHICAGO

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* From the Leon Klein Fund, the Premature Infant Station of the Sarah Morris Hospital for Children and the Nelson Morris Institute for Medical Research of the Michael Reese Hospital.

INTRODUCTION

In the study of the spinal fluid in intracranial hemorrhage of the new-born, premature infants offer perhaps the best material as subjects of investigation, not only for the reason that intracranial hemorrhage occurs so frequently in these infants, but also because of the fact that permission for postmortem examination is more easily obtained than in any other class of hospital patients. The latter is important if clinical observations are to gain significance by correlation with subsequent observations at necropsy.

For a period of one year, while resident pediatrician, I had the opportunity of performing lumbar punctures at the Premature Infant Station of the Sarah Morris Hospital. This station maintains twelve electrically controlled incubators for premature infants and provides graduate nurses for their care and wet nurses to furnish breast milk. Patients are received from the maternity department of the hospital, and the hospital interns call for and bring to the station in an electrically heated ambulance bag (designed for that purpose by the founder of the station, Dr. Julius H. Hess [1]) premature infants from any part of Chicago regardless of the race or of the parents' ability to pay. More complete details regarding the station are given in the communication of Hess and Chamberlain.[2]

My purpose in the study here presented is to correlate the results of lumbar punctures with the observations in the clinic or at necropsy. Other aspects of cerebral hemorrhage in the infants of this series will be dealt with by Hess and Clein [3] in another paper. Somewhat less than half of the lumbar punctures of this series were made during life for the reasons that punctures in living premature infants were delayed until practice on cadavers had shown that the technic to be described would give fairly satisfactory results and that sufficient indication for lumbar puncture was not always present during life. In regard to the fluids obtained post mortem, there is no reason to believe that they change materially in the few minutes immediately following death with respect to the features of the fluid studied here, namely; the clarity of the fluid, its color, the presence or absence of gross or microscopic blood, and the results of the benzidine, van den Bergh and Pandy tests on the fluid.

Originally it was intended to study and compare fluid obtained by ventricular and cisternal as well as by lumbar puncture. It was soon

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1. Hess, J. H.: Ambulance for Transportation of Premature Infants, J. A. M. A. **90**:541 (Feb. 18) 1928.

2. Hess, J. H., and Chamberlain, I. M.: Premature Infants: A Report of Two Hundred and Sixty-Six Consecutive Cases, Am. J. Dis. Child. **34**:571 (Oct.) 1927.

3. Hess, J. H.; Clein, N. C., and Kovan, D.: Unpublished work.

decided to limit the punctures to the lumbar region only for the following reasons: Occasionally at necropsy hemorrhages were found on the cortex of such a nature that it was sometimes difficult to determine whether they were the result of the diagnostic ventricular punctures or had occurred before the punctures were made. Cisternal punctures were abandoned because it was found that most of the fatal hemorrhages occurred about the brain stem in the region of the cisterna magna, and my associates and I wished to avoid any doubt that might arise regarding the possible production of these hemorrhages by the punctures.

It may be said in passing, however, that in this series there was never any positive evidence at necropsy that a significant hemorrhage had occurred as a result of cisternal puncture. The same cannot be said of ventricular puncture.

In one case in this series in which death occurred at the age of 6 weeks from otitis media and athrepsia, the spinal fluid obtained immediately after death was water-clear and contained only a few red blood cells microscopically, not enough to give a positive benzidine reaction. Immediately after the spinal puncture bloody fluid was obtained by ventricular tap, and at necropsy the entire cerebrospinal axis was found bathed in blood, apparently due to a severed cortical vessel and to injury to the choroid plexus. A similar accident was also observed in an infant several months old who had not been born prematurely and who died of acute encephalitis.

It is possible that hemorrhages of the nature described might not occur in living infants due to differences in the pressure relationships between the cerebrospinal fluid and the blood in the cortical vessels or those of the choroid plexus. Nevertheless, these accidents, together with the fact that ventricular puncture is the most uncertain and the most nearly blind method of the three, compelled the employment of diagnostic ventricular puncture only as the last method of choice. Cisternal puncture, it is felt, occupies the middle position of the three methods. It is occasionally easier and usually more nearly certain than lumbar puncture (for reasons to be given subsequently) and is reasonably safe in experienced hands.

UNSUCCESSFUL LUMBAR PUNCTURES

The frequent occurrence of dry taps, or taps contaminated by traumatic blood, is not an unusual source of irritation to pediatricians. In the case of premature infants, these accidents are particularly prone to occur. A study of the spinal canal of such infants has convinced me that by far the most common cause of dry taps or taps contaminated by traumatic blood may be explained as follows: The spinal dura mater, even in the case of premature infants, is a well developed, tough, resistant membrane. Throughout its length and in the lumbar region

particularly, it is loosely attached to the bony wall of the vertebral canal by areolar tissue, and is often separated from this wall by a distance of one or several millimeters. As a consequence, even when a fine needle is introduced, the dura of the posterior wall of the canal may be pushed from its loose attachment across the canal over and against the anterior wall, resulting in a dry tap because the needle never actually entered the subdural space. The mechanism of this is illustrated in figure 1.

If the operator, on feeling the resistance caused by the impingement of his needle against the anterior wall of the canal, separated from it only by two layers of dura mater, continues to exert pressure against the needle, one of several things may happen. The needle pierces the

Fig. 1.—Saggital section of the lumbar portion of the vertebral canal of a premature infant who weighed 925 Gm. at birth and died at the age of 2 hours. The photograph, which is natural size, shows the mechanism of the faulty tap, which was made immediately after death. The needle has pushed the posterior wall of the dura mater against the anterior, pierced both, and entered the highly vascular body of a vertebra, explaining the contamination of the fluid withdrawn by traumatic blood.

posterior layer of dura, which may be under enough tension to slide back along the needle, resulting in a tap which yields the fluid content of the subdural space as it exists, or, as more often happens, both layers of dura are pierced and the needle enters the venous plexus on the anterior wall of the canal or the highly vascular body of a vertebra, and a bloody tap or a tap contaminated by traumatic blood will occur. If the less vascular intervertebral disk is pierced, the tap is usually dry.

With larger needles faulty taps will be made more often, because, even when a sharp needle is used, the ease with which the dura is

pierced varies inversely as the diameter of the needle. This is easily demonstrated by testing strips of dura mater against needles fastened to a balance on which the amount of pressure exerted against the needle may be measured in units of weight at the moment the needle pierces the dura.

The foregoing explanation of faulty taps has been verified repeatedly at necropsy when permission to dispose of the body afterward enabled the performance of radical dissections. I believe that this mechanism explains certain types of faulty taps not only in premature infants but also in older children and occasionally in adults in whom the dura, according to Morris,[4] is practically unattached along the the posterior wall of the vertebral canal.

Higher in the canal, above the lumbar region, separation of the dura from the posterior wall of the canal is less likely to occur because of its closer attachment by the dural cuffs of the shorter intravertebral portions of the spinal nerves leaving the canal in this region. However, while successful spinal taps may occasionally be performed in premature infants at any level of the canal, taps above the lumbar region were avoided whenever possible in living infants for fear of injuring the spinal cord.

In cisternal punctures, faulty taps are not so prone to occur because the tight attachment of the dura mater at the foramen magnum prevents pushing forward of the dura of the posterior wall of the canal.

The only way in which the accident referred to can be avoided is to increase the pressure of the cerebrospinal fluid within the canal so that the posterior dural wall will not be pushed forward by the needle. In some cases of hemorrhage and in most cases of inflammation of the meninges, this is provided for by an increased amount of fluid within the dural sac. The only practical way, however, that has been found for producing this in effect is to have the infant in a sitting position when the puncture is done. The lumbar portion of the dural sac is thus distended by the pressure from above of the column of fluid within it.

An infrequent cause of dry taps is collapse of the dura around the spinal cord or the cauda equina. The collapse may be complete or partial. In one instance, on longitudinal section of the dura, the cord bulged through the opening. Collapse of the dura, when present, usually occurs in extremely dehydrated infants, and in the course of these investigations has been produced experimentally in cadavers who were not dehydrated by drawing off unusually large amounts of spinal fluid, in excess of 4 cc. in premature infants.

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4. Morris: Human Anatomy, ed. 6, edited by C. M. Jackson, Philadelphia, P. Blakiston's Son & Company, 1921, p. 946.

Occasionally an apparently dry tap may be converted into a successful tap merely by rotation of the needle. In such a case, the opening of the needle is uncovered from the dura or nerve filament or bit of exudate or clot against which it was impinged.

In the case of dry taps in premature infants, the other causes of failure to obtain fluid, as listed by Levinson,[5] must not be forgotten. These are: The needle may not have been inserted far enough into the canal; the needle may have been inserted too far and passed through into the vertebral column; the contents of the canal may be too thick to pass through the needle; there may be an absence of fluid in the lower part of the canal due to obstruction above to the circulation of the cerebrospinal fluid, or there may be deformity of the vertebral column.

TECHNIC OF LUMBAR PUNCTURE IN PREMATURE INFANTS

An assistant holds the child, with the back slightly flexed, in an upright sitting position for the reasons already detailed. This position is also advantageous because by it the cramping and resulting cerebral congestion of the child, which Grulee[6] objected to in the procedure usually employed, are avoided.

The skin is prepared with alcohol or 1 per cent mercurochrome-220 soluble, and asepsis is maintained throughout. A fine hypodermic needle (no. 27) is employed. It should be sharp and have a short bevel, and should be fitted up to the beginning of the bevel with an ordinary fine wire obturator. The needle and the syringe mentioned later should be absolutely dry to avoid hemolysis or crenation of such red blood cells as may occur in the fluid withdrawn. A lumbar interspace is chosen, preferably the widest, which is usually the third or fourth, and the needle inserted in the midline through the skin and supraspinous ligament just above the lower spine of the interspace, with a slight inclination upward of the point of the needle. The needle inclines upward not only because the opening between the bodies of the vertebrae is usually somewhat higher than the opening between the spines of the same vertebrae, though not as much as in older children and adults, but also because the dura is less easily pushed forward and more easily pierced if the needle is directed at it at an angle.

The needle is inserted slowly and rotated gently on its long axis as it is pushed forward. This causes a drill-like action which enables the needle to penetrate the dura with greater ease than if the needle were pushed without rotation in the ordinary manner. After the needle has been inserted about 12 or 15 mm., depending on the size of the infant, the obturator is withdrawn and fluid is watched for. If the fluid is not thickened by blood or other substances it appears within from ten to fifteen seconds, depending on the pressure.

If fluid does not appear, the obturator is reintroduced and the needle inserted slightly farther. Often a distinct decrease of pressure against the needle or the sensation of a "snap" may be felt as the needle pierces the dura. If the resistance of the anterior wall of the vertebral canal is felt, the needle is withdrawn and another attempt made. Occasionally, success has been obtained at this point, i. e.,

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5. Levinson, A.: Cerebrospinal Fluid, ed. 2, St. Louis, C. V. Mosby Company, 1923, p. 70.

6. Grulee, C. G.: Treatment of Intracranial Hemorrhage in the New-Born, J. A. M. A. **85**:336 (Aug. 1) 1925.

as soon as resistance is encountered to the passage of the needle, by removing the obturator and attaching a 2 cc. syringe. As the needle is slowly withdrawn the piston is gently pulled on, and not infrequently a point is reached where spinal fluid appears in the syringe. The syringe is useful also in case the fluid comes too rapidly, as there is often difficulty in replacing the fine wire obturator, or if it is replaced fluid may leak around it.

The features of this technic, illustrated in figure 2, are self explanatory.

For the purposes of this study, about 1.25 cc. of spinal fluid was withdrawn, but from 1.5 to 2 cc. may be withdrawn without harm. For therapeutic purposes, usually in the treatment of patients with hemorrhage, the amount of fluid with-

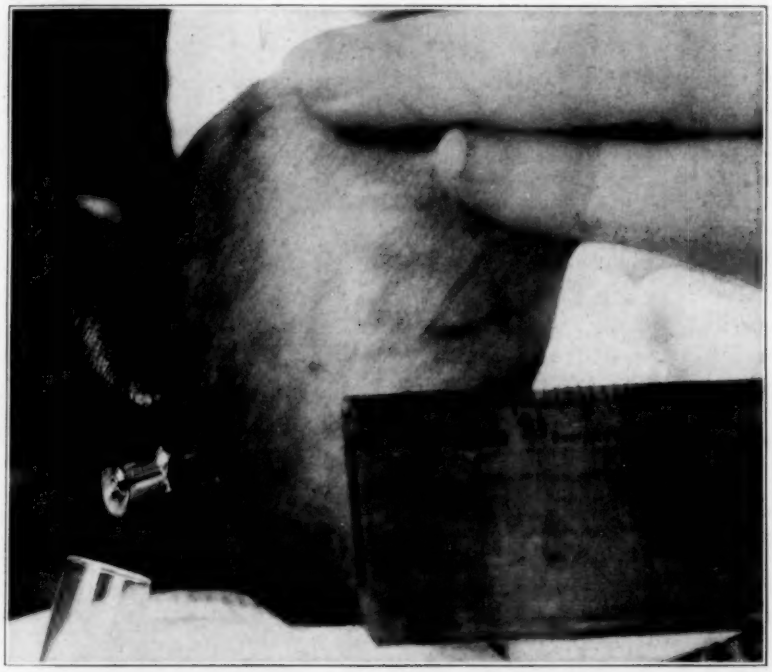

Fig. 2.—Approximately natural size photograph illustrating some features of the technic described. The infant weighed 1,000 Gm. and was 3 hours old at the time of the lumbar puncture.

drawn depends on its pressure and on the clinical indications, such as the effect on a distended or tense fontanel, and more particularly, the behavior of the infant during the procedure.

Possibly 2 cc. of cerebrospinal fluid may seem an excessive amount to remove from a premature infant. However, it must be remembered that the amount of fluid in the cerebrospinal reservoir of an infant is proportionately greater than in an adult. Six cubic centimeters of fluid can usually be withdrawn after death by means of a needle and syringe from the spinal canal of a premature infant weighing 1,200 Gm. Mestrezat,[7] in reviewing the literature on the subject, stated

7. Mestrezat, W.: Le liquide céphalo-rachidien, Thèse à la Faculté de Medécine de Montpellier, 1911.

that from 60 to 150 cc. of cerebrospinal fluid may be withdrawn after death from adult cadavers. If one takes the maximum amount and applies it to a man of average weight (70 Kg.), a premature infant weighing 1.2 Kg. should yield proportionately only 2.5 cc. of fluid. Practically almost three times as much is obtained. To be sure, if 2 cc. is withdrawn from a living premature infant, the amount is proportionately more than twice as large as is usually withdrawn for diagnostic purposes from an adult. Regardless of theoretical considerations, however, premature infants do not show ill effects resulting from the removal of such amounts of fluid as already stated.

The fluid, if clear, was usually divided as follows: one drop each for the cell count and Pandy test; two drops for the benzidine reaction; all the remainder (except as otherwise noted) for the determination of the icterus index, and, after this was done, 0.25 cc. for the direct van den Bergh test and 0.75 cc. or as little as 0.5 cc. for the indirect van den Bergh test. The technic and significance of the van den Bergh reactions and the icterus index will be discussed subsequently.

After the puncture the infant should at once be placed on the side to avoid leakage of cerebrospinal fluid along the needle track, and the site of the puncture protected by a small cotton-collodion dressing.

This technic has not entirely done away with dry taps or taps contaminated by traumatic blood, but it has reduced the number of faulty taps in cases proved by autopsy from 35 to 20 per cent. With more experience, further improvement may be expected. In living infants varying in weight from 885 Gm. and in age from one-half hour upward punctures have been performed, in some cases repeatedly. Untoward results have not been seen which could be attributed to the fact that the infant was sitting upright during the puncture or to the puncture itself. On the other hand, in clinically undoubted cases of cerebral hemorrhage (some of which were subsequently proved by autopsy), my associates and I have observed several instances in which, when this technic was used, the spinal canal was entered with ease, and if a comparatively large amount of bloody fluid was withdrawn the infant's life was either significantly prolonged or preserved, at least until the time that this article was written.

RELATIONSHIP OF THE PRESENCE OR ABSENCE OF BLOOD IN THE CEREBROSPINAL FLUID TO THE NECROPSY OBSERVATIONS

(*a*) *Cerebral Hemorrhage Present at Necropsy.*—In this discussion only the seventy cases in which necropsies were performed will be considered. Since my associates and I were particularly interested in hemorrhages at the cerebellomedullary angle (because they were so often fatal), whenever circumstances permitted a vertical incision was made in the nuchal fossa and the tissues of the neck dissected aside down to the atlanto-occipital membrane. The posterior arch of the atlas was removed without incising the dura, and the subtentorial portion of the occipital bone dissected away extradurally. A dry field was secured and the dura incised and reflected. This resulted in a

good exposure of the cerebellum and upper surface of the medulla oblongata before the cranial contents were disturbed by dissection above the tentorium. The remainder of the dissection was similar to that of Meyer and Hauch's [8] elaboration of von Beneke's [9] technic, except that the brain was usually removed intact from the cranial cavity instead of each hemisphere and the cerebellum and brain stem separately.

The great majority of the hemorrhages were subpial or subarachnoid. Only one hemorrhage could be attributed to a tentorial tear, and in another case hemorrhage was due to tearing of the great vein of Galen. These observations are in accord with those of Ylppö,[10] who commented on the frequency of subpial hemorrhage and the fact that tentorial tears are uncommon in premature infants as compared with full term infants, in whom the skulls are harder.

Table 1 indicates that in this series of seventy necropsies cerebral hemorrhage was present in twenty-six, or 37 per cent. The hemorrhages were of such a nature that from their location they were presumably

TABLE 1.—*Cerebral Hemorrhage Present at Necropsy* *

	Number of Cases	Per Cent of Cases	Average Age of Patient in Days
Spinal fluid grossly bloody or hazy	19	73	1
Spinal fluid clear	7	27	8

* Total cases, 26.

the cause of death, or from their size might reasonably be supposed to have influenced the condition found at the examination of the cerebrospinal fluid. Cases showing only an occasional minute subpial hemorrhage are not included.

Of the twenty-six infants with hemorrhage at birth the spinal fluid was grossly bloody or contained a sufficient number of red blood cells (about 500 per cubic millimeter) to give the fluid a hazy appearance in nineteen, or 73 per cent. This is of great interest because it is equivalent to saying that even when cerebral hemorrhage is present the spinal fluid will be macroscopically bloody in only seven out of ten cases, or, if patients only 1 day of age or less are considered, in eight out of ten cases.

Those cases in which clear cerebrospinal fluid was obtained in the presence of cerebral hemorrhage will be discussed in detail subsequently.

8. Meyer, L., and Hauch, E.: Les ruptures de la dure-mère cranienne chez les noveau-nés, Arch. mens. d'obst. et de gynéc. **1**:246, 912.

9. Von Beneke, R.: Ueber Tentoriumzerreisung bei der Geburt, Verhandl. d. deutsch. path. Gesellsch. **14**:128, 1910.

10. Ylppö, A.: Pathologisch-anatomische Studien bei Frühgeborenen, Ztschr. f. Kinderh. **20**:212, 1919.

(*b*) *Cerebral Hemorrhage Not Present at Necropsy.*—Table 2 illustrates the frequency of bloody taps in patients not suffering from cerebral hemorrhage. Of forty-three such cases, grossly bloody or hazy fluid was found in thirteen, or 31 per cent. This is interesting in comparison with the observations of Sharpe and Maclaire[11] of bloody fluid in 9 per cent of all new-born infants, mostly full term and punctured during the first day of life. Roberts[12] found macroscopically bloody fluid in 32 per cent of fifty-six new-born premature infants. The series quoted was uncontrolled by any significant number of autopsies, and this illustrates the great possibility of error in making a diagnosis of intracranial hemorrhage on the basis of grossly bloody spinal fluid alone.

TABLE 2.—*Cerebral Hemorrhage not Present at Necropsy* *

	Number of Cases	Per Cent of Cases	Average Age of Patient in Days
Spinal fluid grossly bloody or hazy	13	31	5
Spinal fluid clear	29	69	32

* Total cases, 42.

TABLE 3.—*Cerebral Hemorrhage not Present at Necropsy (Spinal Fluid Water-Clear)* *

	Number of Cases	Per Cent of Cases	Average Age of Patient in Days
Microscopic blood present	18	62	23
Microscopic blood absent	11	38	47

* Total cases, 29.

Two new-born premature infants from whom hazy spinal fluids (due to the presence of red blood cells) were obtained shortly before death are not included in tables 1 and 2. In both cases at necropsy, macroscopic hemorrhage was not found, but there was marked congestion of the meninges to which the presence of red blood cells in the spinal fluid was doubtless due.

Table 3 contains those cases in table 2 in which intracranial hemorrhage was not found at necropsy and the spinal fluid was water-clear. To avoid confusion it should be kept in mind that the term "water-

11. Sharpe, W., and Maclaire, S.: Intracranial Hemorrhage in the New-Born, J. A. M. A. **88**:332 (Jan. 30) 1926. In this article will be found references to their other publications on the same subject.

12. Roberts, M. H.: Spinal Fluid in the New-Born, With Especial Reference to Intracranial Hemorrhage, J. A. M. A. **85**:500 (Aug. 15) 1925; Intracranial Hemorrhage in the New-Born, South. M. J. **20**:642 (Aug.) 1927.

clear," which I prefer to the somewhat less accurate but more frequently used term "crystal-clear" does not also mean "colorless." The color of the fluid will be considered under the section on xanthochromia.

Of the twenty-nine cases of table 3, microscopic blood was present in eighteen, or 62 per cent or in about three fifths of the cases. A comparison of tables 2 and 3 will show that when cerebral hemorrhage is not present, the older the patient the less likely is a bloody tap to be produced and the less frequently will microscopic red blood cells be present in the fluid. Thus the average age of the patients in this class at the time of puncture when the taps were grossly bloody was 5 days; the average age at which microscopic blood alone was found was 23 days and the average age at which blood was not present was 47 days.

In the spinal fluids reported on in table 3, the red blood cells were counted after a few drops of cerebrospinal fluid obtained in a separate test tube toward the end of the tap (to avoid contamination with traumatic blood as a result of the passage of the needle through the tissues overlying the spinal dura) were agitated with a current of air blown through a pipet. If the fluid was not macroscopically bloody, it was examined undiluted on the field of an ordinary blood-counting chamber. If the cells were few they were counted under the high power lens of the microscope which was also used to observe the degree of crenation. The entire ruled field of the counting chamber 9 sq. mm., was examined before a fluid free from blood was diagnosed. In only three instances were red blood cells not present in the fluid of an infant, aged 4 days or under. In one case the infant was 4 days of age; in another, 28 hours and in the third, 22 hours. This bears out Robert's [13] statement that one rarely finds a spinal fluid in a new-born infant which does not contain at least an occasional red blood cell if sufficient diligence is expended in the search.

(*c*) *Significance of Crenated Cells.*—Crenated cells were not observed in this series in infants over 17 days of age at the time of the first lumbar puncture. As a rule, the older the child the less the number of red blood cells in the spinal fluid and the greater the percentage of crenated cells. Crenation probably indicates that the cells have been in the spinal fluid for some time, presumably as the result of previous diapedesis, rhexis (capillary hemorrhage) or grosser forms of hemorrhage. Crenated cells are of only suggestive value in the diagnosis of intracranial hemorrhage, as they are occasionally found in large numbers in the spinal fluid when gross hemorrhage cannot be demonstrated and as they may be few in cases showing extensive hemorrhage at necropsy.

13. Roberts (footnote 12, first reference).

(*d*) *Significance of the Benzidine Test.*—The benzidine reaction was present, as a rule, in proportion to and varying in intensity with the number of red blood cells found in the fluid. The test usually began to show as a faint trace when the cells numbered about 300 per c. mm. In performing the test it was found convenient to use the tablets of benzidine and sodium perborate described by D. Roberts.[14] The results are uniform, and a rough quantitative estimation of the amount of blood present in the fluid may be obtained.

The presence of hemoglobin in solution in the supernatant fluid after centrifugalizing bloody fluid obtained by lumbar puncture, as evidenced by a positive benzidine reaction, was of some value in differentiating between traumatically bloody fluid and that bloody because of cerebral hemorrhage. In ten instances of bloody taps in patients who did not show evidence of intracranial hemorrhage at postmortem performed immediately after the tap, the benzidine reaction on the supernatant fluid was negative. These patients varied in age from 2 hours to 6 months. In twelve patients with intracranial hemorrhage, in whom the condition was proved at autopsy, after the bloody fluid obtained by lumbar puncture was centrifugalized, a positive benzidine reaction was obtained from the supernatant fluid in six cases, or 50 per cent. These patients were all under 1½ days of age.

For this test to have value, great care must be taken to have the instruments used in performing the tap—the needle, syringe and centrifuge tube—dry to avoid hemolysis. For the same reason the centrifuge should be running smoothly and the fluid should be centrifugalized without delay.

(*e*) *Significance of the Pandy Test.*—The Pandy reaction varied in intensity with the number of red blood cells present in the cerebrospinal fluid, which was probably also an indication of the amount of dilution of the spinal fluid by blood plasma. The Pandy reaction was often positive when red blood cells were not present, and in one instance it was negative when the red blood cells numbered 150 per c. mm. Ordinarily it became less positive as the interval following its first appearance increased.

The relationship of the Pandy test in fluids free from blood to the degree of xanthochromia will be considered under the discussion of the latter subject.

INTRACRANIAL HEMORRHAGE WITH SPINAL FLUID FREE FROM BLOOD ON GROSS EXAMINATION

Spinal fluid free from blood may reasonably be expected to occur in intracranial epidural hemorrhage or in hemorrhage within the brain

14. Roberts, D.: A Benzidine Tablet Test for Occult Blood, J. A. M. A. **65**:244 (July 17) 1915.

tissue. Epidural hemorrhage sometimes occurs in full-term infants but rarely in premature infants, possibly on account of the softness of the bones of the skull. In this series of premature infants, it occasionally occurred in the form of petechiae, which was also the form epidural hemorrhage took in Ylppö's [10] series of premature infants.

Interstitial intracranial hemorrhage was not observed in this series except in some cases in minute amounts from the small vessels of the cortex or beneath the ependyma.

Subarachnoid and subpial hemorrhages may, however, occur without the appearance of gross blood in the spinal fluid, and these types are the most common forms of cerebral hemorrhage in premature infants.

Henschen [15] stated that in his experience, when hemorrhage at birth is suspected, one lumbar puncture is not sufficient, for in spite of previous hemorrhage the fluid may be clear. Green [16] reported the case of an infant, aged 7 days, who was delivered by forceps. Clinical symptoms of hemorrhage developed on the fourth day. Lumbar puncture at that time yielded clear fluid. The child died three days later, and at necropsy an extensive supratentorial hemorrhage was found. Green attributed the clear fluid to the supratentorial position of the hemorrhage. Blanco and Paperini [17] also stated that the spinal fluid may be clear if the hemorrhage is supratentorial. Levinson [18] reported two cases in premature infants of fairly extensive infratentorial subarachnoid hemorrhage of the cerebellum. In these cases lumbar punctures were made fourteen and twenty-one days, respectively, after birth. Both fluids were yellow and contained a microscopic number of red blood cells. The benzidine test was negative in the first case and positive in the second.

Table 4 lists, in the order of age, the cases in my series in which subpial or subarachnoid hemorrhage occurred without the appearance of gross blood in the spinal fluid.

Case 1.—A colored premature infant, a girl, of unknown gestation, weighed 885 Gm. at birth and died at the age of 8 hours. The child was cyanotic, and the diagnosis was considered as resting between atelectasis and cerebral hemorrhage. A lumbar puncture just before death yielded a clear, faintly yellow fluid giving a positive benzidine test and containing 460 red blood cells per cubic millimeter, about 10 per cent of which were crenated. At autopsy a layer of

15. Henschen, K.: Diagnostik und Operation der traumatischen Subduralblutung, Arch. f. klin. Chir. **99**:5, 1912. Die diagnostische und therapeutische Fontanellaspiration des subduralen Geburtshämatoms der Neugeborene, Zentralbl. f. Gynäk. **37**:925 (June 14) 1913.

16. Green, R. M.: Intracranial Hemorrhage in the New-Born, Boston M. & S. J. **170**:682 (April 30) 1914.

17. Blanco, L. V., and Paperini, H.: Meningeal Hemorrhage in the New-Born, J. A. M. A. **87**:1261 (Oct. 16) 1926.

18. Levinson, A.; Greengard, J., and Lifvendahl, R.: Cerebrospinal Fluid in the New-Born, Am. J. Dis. Child. **32**:208 (Aug.) 1926.

blood clot about 2 mm. thick was found beneath the pia-arachnoid covering the upper surface of the cerebellum. Because of the failure of the hemorrhage to involve vital structures it was not considered to have been the cause of the infant's death. This was attributed to atelectasis, which was extensive.

CASE 2.—This case represents the usual type of pial hemorrhage found in premature infants, i. e., petechial hemorrhages beneath or within the pia. In this case, the hemorrhages were far more numerous than usual. The twin of this infant, who died at about the same time, had yielded a bloody fluid at lumbar puncture immediately after death. The conditions found at necropsy were the same except that in this case the hemorrhages were larger and had broken through into the subarachnoid space rather extensively.

CASE 3.—A premature infant, a boy, of six and one-half months' gestation, who weighed 1,250 Gm., was delivered in a normal manner after a prolonged labor of sixteen hours. He was listless, had intermittent cyanotic attacks and died

TABLE 4.—*Subpial Hemorrhage Without Grossly Bloody Cerebrospinal Fluid*

Case	Age in Days	Description of the Hemorrhage	Color of Spinal Fluid	Red Blood Cells per C.Mm.	Benzidine Reaction
1	⅛	Moderate, covering entire upper surface of cerebellum	Faintly yellow	460 (10% crenated)	Positive
2	⅜	Extensive, scattered, petechial over both hemispheres and cerebellum	Faintly yellow	270	Positive
3	1	Large, at angle between cerebellum and medulla oblongata	Golden yellow	Present	Positive
4	5	Extensive on lower surface of cerebellum and anterior surface of pons	Deep yellow	None	Negative
5	10	Extensive on upper surface and part of lower surface of cerebellum	Icterus index 4	20 (traumatic)	Negative
6	14	Thick layer covering the superior and inferior semilunar lobes and the horizontal sulcus of the cerebellum	Icterus index 3	20 (few crenated)	Faint trace
7	22	Extensive on lower surface of cerebellum	Moderately yellow	Few; crenated	Positive
8*	34	Layer of well organized dark clot extending from beneath the pons to and encircling the junction of the spinal cord and medulla oblongata up to and beneath the lower surface of cerebellum	Colorless	2	Negative
9*	35	Large, involving the lower surface of the cerebellum; well organized without macroscopic blood pigment	Very faintly yellow	Few	Faint trace

* The infant was not born prematurely.

twenty-four hours after birth. A lumbar puncture was done immediately after death and 0.5 cc. of clear, golden yellow fluid, apparently under pressure, spurted from the needle and then the flow suddenly ceased. This fluid contained a few red blood cells macroscopically and gave a positive benzidine reaction. A ventricular puncture was made immediately after the spinal puncture, and an unusually large amount of cerebrospinal fluid moderately and uniformly diluted by blood spurted from the needle. At necropsy, a large subarachnoid clot was found in the cerebellobulbar angle extending laterally over the lower surface of the cerebellum. A distinct though moderate degree of internal hydrocephalus was present. It seemed apparent that the hemorrhage had caused a partial blocking of the foramina leading from the fourth ventricle (Magendie and Luschka), resulting in an early internal hydrocephalus. When the intraspinal pressure was partially relieved by the lumbar puncture, the clot, the cerebellum and the medulla oblongata were forced downward into the foramen magnum by

the unbalanced pressure of the fluid in the ventricles above. The plugging of the foramen magnum caused the sudden cessation of flow through the needle at the time of lumbar puncture that has already been described. If such an accident had happened during life, a fatality might possibly have resulted. This indicates the care with which lumbar puncture should be performed in the presence of a hydrocephalus.

Case 4.—An extensive hemorrhage had occurred in this infant, but red blood cells could not be found in the spinal fluid when the infant was 5 days old, and the fluid gave a negative benzidine reaction. This patient suffered from kern icterus and possibly this condition was in some way related to the disappearance

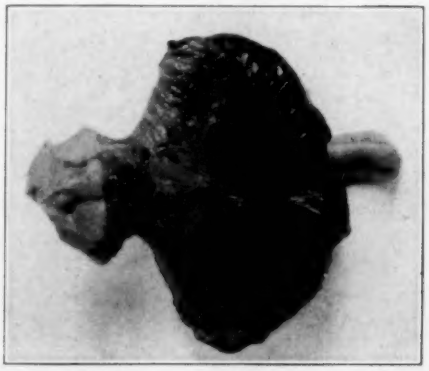

Fig. 3.—Natural size photograph showing the hemorrhage on the upper surface of the cerebellum of case 5 of table 4.

Fig. 4.—Natural size photograph of a saggital section of the portion of the brain illustrated in figure 4. This demonstrates how even a large hemorrhage may be delimited by the pia-arachnoid membrane, and shows clearly how an internal hydrocephalus may be produced when such hemorrhages are limited above by the tentorium causing pressure to be exerted downward on the cerebral aqueduct, or the fourth ventricle and its foramina. Such pressure, when transmitted to the medulla oblongata, is also responsible for the cyanotic attacks so characteristic of subtentorial hemorrhage.

of red blood cells and hemoglobin from the spinal fluid, if one assumes that they had appeared there at the time of the hemorrhage.

Case 5 (figs. 3 and 4).—A premature colored infant of about thirty weeks' gestation weighed 1,750 Gm. At birth, cerebral hemorrhage was diagnosed, and lumbar puncture yielded a bloody fluid, apparently not traumatic and containing

3,600 red blood cells per cubic millimeter. About one eighth of these cells were crenated, and the benzidine test on the supernatant fluid after centrifugalizing was negative. Ten days later the patient died, and at necropsy there was found a fairly extensive hemorrhage involving the upper surface of the cerebellum and part of the lower as well as a portion of the brain stem. A lumbar puncture made immediately post mortem had yielded a clear fluid containing only 20 red blood cells per cubic millimeter, and these were unquestionably of traumatic origin. The observations are in agreement with those of Schwartz,[19] who stated that the red blood cells following hemorrhage disappear rapidly from the spinal fluid, none being left at the end of seven days, as a maximum.

Cases 6 and 7.—These cases represent types of rather large subtentorial hemorrhage. The observation of blood in the spinal fluid on gross examination could hardly be expected on account of the time that had elapsed between the occurrence of the hemorrhage at birth and the age of the child at the time of puncture. In case 6, cerebral hemorrhage was not suspected during life; in case 7, it was.

Case 8.—While the infant was not premature, this case is included in the table because of the interest attached to the fact that the condition was diagnosed during life and the diagnosis adhered to regardless of the fact that a normal spinal fluid was obtained. The correct diagnosis was made because the symptoms shown by this infant were identical with those usually found in premature infants with subtentorial hemorrhage involving the medulla oblongata, and from premature infants it had been learned that a fatal cerebral hemorrhage did not necessarily result in blood in the spinal fluid. This case has been reported in detail in another paper.[20]

Case 9.—The infant in case 9, also not born prematurely, is of interest because it illustrates how completely a blood clot may be organized at the age of 35 days.

It is noteworthy that the benzidine reaction was positive in six of the nine cases here recorded. The significance of the color of the spinal fluid in relationship to cerebral hemorrhage will be discussed subsequently in the section dealing with xanthochromia.

MECHANISM OF SUCH HEMORRHAGES

The mechanism of subpial or subarachnoid hemorrhage without the appearance of grossly bloody, or, more rarely, microscopically bloody, spinal fluid can be understood only with a clear conception of the relationships of these two cerebral membranes. The pia mater [21] lies everywhere in close contact with the external surface of the brain and extends also into the depths of the cerebral sulci. In addition, it penetrates into the transverse cerebral fissure (between the cerebellum,

19. Schwartz, E.: Ueber Xanthochromie des Liquor cerebrospinalis, Deutsche Ztschr. f. Chir., **124**:346, 1913.

20. Glaser, J.: Delayed Death as a Result of Birth Cerebral Hemorrhage, M. Clin. N. Amer., to be published.

21. Spalteholz, W.: Hand Atlas of Human Anatomy, trans. from the fourth German edition by L. F. Barker, second English ed.; Philadelphia, J. B. Lippincott Company, 1906, vol. 3, p. 654.

mesencephalon and thalamencephalon below and the occipital lobes of the cerebral hemispheres above) and the transverse cerebellar fissure (between the cerebellum and the medulla oblongata) to form the choroid tela of the third and fourth ventricles, respectively. The arachnoid may be described as a membrane closely applied to the dura. From the inner surface of the arachnoid project numerous delicate trabeculae which merge with the pia mater. Between these two membranes the cerebrospinal fluid circulates in a system of continuous yet partially interrupted

Fig. 5.—Section from near the edge of the hemorrhage in case 4 of table 4. Much of the sharpness of outline of the stained section is lost in the photograph. *A* is part of the cerebellum; *B* marks the area of the hemorrhage, in which whole red cells as well as darker masses, which represent free blood pigment, may be clearly seen. *C* is the pia-arachnoid membrane, the vessels of which are greatly congested; × 65.

spaces in the meshes of the arachnoid trabeculae. "These meshes," Weed [22] wrote, "are of various sizes, increasing from fine, reticular spaces over the cerebral hemispheres to more widely calibrated channels in the cerebral sulci and about the spinal cord, and reaching their maximum in the cisternal dilatations about the cerebello-bulbar angle. In the wide

22. Weed, L. H.: The Cerebrospinal Fluid, Physiol. Rev. **2**:172, 1922.

channels of this subarachnoid meshwork the cerebrospinal fluid is obstructed but little in its circulation, but in the smaller meshes the flow of the liquid is slowed."

Figure 5 is a photomicrograph of a subpial hemorrhage from case 4 of table 4. It illustrates a hemorrhage between the cortical brain substance and the pia mater. Under the microscope, the shape of the red cells can be easily recognized, and the hemorrhage is seen as prevented from any significant admixture with the cerebrospinal fluid in the subarachnoid spaces by the limiting membrane of the pia-arachnoid.

The exact source of these hemorrhages is difficult to determine, and even in adults with subarachnoid hemorrhage in whom the structures are larger and firmer, the ruptured vessel is not always found.[23] It was not found in any of our series, though presumably it might have if serial sections had been studied. Doubtless the hemorrhages arise from the small blood vessels of the pia, which is a vascular membrane. Subpial hemorrhages are probably always accompanied by some degree of subarachnoid hemorrhage with the presence of varying numbers of red blood cells in the cerebrospinal fluid. Macroscopic blood is not found in some cases, probably because of the formation of clots during the oozing of the blood from the site of hemorrhage facilitated by the fine network of subarachnoid trabeculae in certain localities, as already described. This probably explains the fact noted by Henschen[24] that cerebral hemorrhages in infants (other than those due to sinus tears) have a tendency to remain localized in the place of origin.

VALUE OF BLOODY FLUIDS IN DIAGNOSIS

Tables 1, 2, 3 and 4 bring up the question of the value of bloody spinal fluid obtained by lumbar puncture in the diagnosis of cerebral hemorrhage of infancy. Opinion on this subject, as expressed in the literature, is divided. Green,[16] Brady,[25] Roberts[13] and Sharpe and Maclaire[11] stated that the finding of bloody cerebrospinal fluid is reliable evidence of intracranial hemorrhage. A contrary opinion is expressed by Lippman,[26] Grulee,[6] Ford[27] and Levinson.[18] My experience is in agreement with the latter group of authors.

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23. Symonds, C. P.: Spontaneous Subarachnoid Hemorrhage, Quart. J. Med. **18**:93 (Oct.) 1924. Munck, W.: Subarachnoid Hemorrhage from the Medico-legal Point of View, J. Nerv. & Ment. Dis. **65**:484 (May) 1927.

24. Henschen (footnote 15, reference 2).

25. Brady, J. M.: Lumbar Puncture in Meningeal Hemorrhage of the New-Born, J. A. M. A. **71**:347 (Aug. 3) 1918.

26. Lippman, M. J.: Meningeal Hemorrhage in the New-Born, New York M. J. **103**:263 (Feb. 5) 1916.

27. Ford, E. R.: Cerebral Birth Injuries and Their Results, Medicine **5**:121, 1926.

It is commonly stated [13] that traumatic blood may be distinguished from blood in the spinal fluid due to a preexisting pathologic condition by the facts that in the former instance the spinal fluid is streaked with blood and clears gradually as the fluid is withdrawn. While these facts are usually true, and although to them I have added the assistance of the benzidine test on the supernatant fluid after centrifugalization, at times it was found impossible to rule out trauma as a source of bloody taps, and the younger and smaller the infant the more often this has occurred. In considering whether or not a bloody tap is due to the trauma of the puncture, in addition to the foregoing facts, the technic, experience and judgment of the physician are of the greatest importance. When a proper technic is employed and a physician experienced in its use feels the needle pierce the dura at the first attempt, and, without having felt the needle impinge against any other obstruction, he withdraws the obturator and obtains a fluid of uniformly maintained appearance, then he may be almost but never absolutely certain (because he is employing a blind procedure) that the tap is free from traumatic blood.

My opinion as regards the presence of blood is that the evidence obtained by lumbar puncture cannot be considered as absolutely positive either for or against the presence of intracranial hemorrhage. Especially is this true when, as already shown, it is considered that bloodless spinal fluid may be found in the presence of fresh intracranial hemorrhage. Other facts, such as the color of the spinal fluid and its chemical reactions, which will be discussed next, and the results of repeated spinal punctures, must be considered.

XANTHOCHROMIA

Xanthochromia, in this discussion, refers to the presence of a yellow spinal fluid, the color of which is not due to the intraspinal administration of yellow substances, such as dyes or serums, the presence of hemoglobin in solution, or of red blood cells in microscopic numbers. For the latter condition, the useful term, "erythrochromia," has been employed by Mestrezat.[7]

According to Leschke,[28] yellow spinal fluid was first described by Busch in 1897, who noted its occurrence at necropsy in the lateral ventricles of a patient who died of a sarcoma involving the third and fourth ventricles, and by Schroeder in 1899, who observed xanthochromia in the spinal fluid of a patient with a diffuse sarcoma of the brain and spinal cord. Attention was not greatly attracted to the phenomenon

28. Leschke, E.: Ueber die Gelbfärbung (Xanthochromie) der Zerebrospinalflüssigkeit, Deutsche med. Wchnschr. **47**:376 (April 7) 1921.

of xanthochromia until 1903, when Froin [29] described the finding of clear yellow spinal fluid with increased protein content in which massive coagulation occurred on standing. This was shown to occur practically only in cases in which there was an obstruction in the spinal canal causing the formation of a culdesac below the level of the obstruction. The fluid withdrawn from such a culdesac is ordinarily yellow and contains increased protein due to the transudation of serum or plasma which probably contributes to the yellow color. Pigment is also supplied by the breaking down of red cells in the fluid of the sac. "Froin's syndrome," as the combination of yellow colored fluid with increased protein content which coagulated on standing, came to be called, was not observed in this series. The literature on the subject has been reviewed by Mix,[30] by Sprunt and Walker [31] and in 1923 by Scully,[32] who stated that more than 350 cases of xanthochromia had been reported up to that time in association with pressure on the cord, hemorrhagic inflammation and hemorrhage into the spinal fluid. Not all of these cases showed Froin's syndrome, however.

In 1920, Abt and Tumpeer [33] described xanthochromia due to a meningo-encephalitis, with numerous subpial hemorrhages as the source of coloration, in a premature infant of eight months' gestation who lived thirty-seven days.

More recently, Roberts [13] and Levinson [16] have pointed out the frequent presence of xanthochromia in the new-born. In Roberts' series of 423 new-born infants, no fluid was obtained which was absolutely colorless, as is normal with adults and older children. All showed some degree of pigmentation varying from a pale straw color to a deep yellow. In Levinson's series of 100 cases, only 12 patients yielded colorless spinal fluid.

In a series of 500 new-born infants, Sharpe and Maclaire [11] found forty-five bloody or blood tinged or yellow fluids. Apparently, xanthochromia occurred in less than 9 per cent of their cases.

Before proceeding with the discussion of xanthochromia as it occurred in this series, I shall describe the method by which the degree of xanthochromia was determined quantitatively.

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29. Froin, G.: Inflammations méningées avec réactions chromatique, fibrineuse et cytologique du liquide céphalorachidien, Gaz. d. hôp. **76**:1005 (Sept. 3) 1903.

30. Mix, C. L.: Spontaneous Massive Coagulation of Cerebrospinal Fluid with Xanthochromia, Surgical Clinics of John B. Murphy **4**:17, 1915.

31. Sprunt, T. P., and Walker, J. E.: Significance of Xanthochromia of the Cerebrospinal Fluid, Bull. Johns Hopkins Hosp. **28**:80, 1917.

32. Scully, F. J.: Yellow Spinal Fluid, Its Origin and Significance, Arch. Neurol. & Psychiat. **10**:83 (Oct.-Dec.) 1923.

33. Abt, I. A., and Tumpeer, I. H.: The Significance of Xanthochromia of the Cerebrospinal Fluid, Am. J. Dis. Child. **20**:153 (Sept.) 1920.

THE ICTERUS INDEX OF CEREBROSPINAL FLUID

In 1920 and 1921, Meulengracht,[34] using potassium dichromate in a dilution of 1 : 10,000, which has a color practically identical with that of pure bilirubin in solution, described a method for determining the degree of pigmentation of blood plasma by diluting the plasma with physiologic sodium chloride solution until the color was identical with that of the standard solution. The amount of dilution of the plasma required for this is a quantitative measure of the depth of color of the plasma. The method was further modified by Maue,[35] who studied the subject at the suggestion of Stettin.[36] Maue simplified Meulengracht's technic by using blood serum instead of plasma and employed a colorimeter for comparing the depth of color of the unknown serum with that of the standard solution. From the colorimeter reading, the number of times it is necessary to dilute the unknown solution to match the color of the standard solution may be easily calculated. This figure was termed the "icterus index" of the fluid by Stettin. The work of Maue and Stettin was further developed by Bernheim,[37] to whom reference is made for a detailed study of the icterus index of the blood serum and the part which other body pigments may take in relationship to this.

The technic employed for this study was described by Brown.[38] Briefly stated, it consists of comparing in a colorimeter the yellow spinal fluid in a test tube of the same composition and diameter as sealed standard tubes containing various dilutions of potassium dichromate. Each of these sealed tubes has etched on its surface a number which represents its "icterus index." For example, the standard tube containing potassium dichromatic in an aqueous solution of 1 : 10,000 has an icterus index of 1. Xanthochromia is best studied in daylight. A faint yellow color of the spinal fluid, when it is examined under the usual type of artificial light, may escape notice.

Practically all the determinations of the icterus indexes of this series and the van den Bergh tests, to be discussed later, were made by Miss

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34. Meulengracht, E.: Die klinische Bedeutung der Gallenfarbstoff im Blutserum, Deutsches Arch. f. klin. Med. **132**:285 (July 13) 1920; Ein Bilirubinkolorimeter behufs klinischer Bestimmung der Bilirubinmenge im Blute, ibid. **137**: 38, 1921.

35. Maue, H. P.: Icterus Index of the Blood Serum, Surg. Gynec. Obst. **34**:752, 1922.

36. Stettin, De W.: The Surgical Value of the Estimation of the Bile Pigmentation (Icterus Index) of the Blood Serum, Ann. Surg. **76**:191, 1922.

37. Bernheim, A. R.: The Icterus Index (A Quantitative Estimation of Bilirubinemia), J. A. M. A. **82**:291 (Jan. 26) 1924; The Significance of Variations of Bilirubinemia, Arch. Path. **1**:747 (May) 1926.

38. Brown, A. L.: A Rapid Clinical Method for the Determination of the Icterus Index, Arch. Path. **3**:409 (March) 1927.

Marie Andersch of the Department of Chemistry of the Nelson Morris Institute. In the determination of the icterus index, it was noted that in the great majority of cases the quality of the color of the spinal fluids of low icterus index was almost, if not exactly, identical with the colors of the standard solutions. With more deeply colored spinal fluids, the quality of the color was not infrequently slightly different, and the icterus index could be determined with much greater accuracy if the spinal fluid were diluted with physiologic sodium chloride solution until its color approximated an icterus index of 2 or 3.

The only recorded observations of the icterus index of cerebrospinal fluid of which I am aware are those of Spurling and Maddock [39] in the study of xanthochromia accompanying tumors of the brain. It is interesting to note that the icterus index in their series rarely exceeded 1,

TABLE 5.—*Relationship of the Age of the Premature Infant to the Icterus Index of the Cerebrospinal Fluid* *

Age in Days	Total Cases of Series		Only Cases in Which Autopsy Was Performed; Cerebral Hemorrhage Not Present	
	Number of Cases	Average Icterus Index	Number of Cases	Average Icterus Index
1 or under	8	1	4	< 1
2 to 7	9	2	3	1½
8 to 14	13	3½	3	2½
15 to 21	3	1½	2	1
22 to 28	9	1½	3	< 1
29 to 59	5	< 1	1	< 1
60 or over	5	0	5	0
Total	52		21	

* The spinal fluid was water-clear; the benzidine test negative.

while in this series, although the majority of icterus indexes were 1 or less, indexes of 2 and 3 were not uncommon and indexes of 4, 5 and 11 were recorded.

THE RELATIONSHIP OF AGE TO THE DEGREE OF XANTHOCHROMIA (ICTERUS INDEX) OF THE CEREBROSPINAL FLUID

To rule out the possibility of any significant contribution to the color of the fluid by hemolysis, the color of fifty-two water-clear spinal fluids giving a negative benzidine reaction, was studied. The relationship between the age of the patient and the color of the fluid is recorded in table 5.

Colorless fluids were found in five instances. These patients were 60 days of age or over. The most nearly colorless xanthochromatic fluid of the series occurred in a child, aged 8 days, who weighed 2,070 Gm.

39. Spurling, R. G., and Maddock, C. L.: Cerebrospinal Fluid in Tumor of the Brain, Arch. Neurol & Psychiat. **14**:54 (July) 1925.

It was necessary to compare this infant's cerebrospinal fluid with an equal amount of distilled water in another test tube of the same size and composition in order to detect a faint yellow tint in the specimen of spinal fluid. The finding of such a pale fluid suggests the possibility that colorless fluids may occur under the age of 60 days though they were not encountered in this series.[40] The universal occurrence of xanthochromia in new-born premature infants is strongly suggested by our studies.

The oldest infant in this series in whom xanthochromia was observed was 42 days of age. This patient was of thirty-six weeks' gestation and weighed 1,510 Gm. at the time of death, which occurred from septicemia secondary to a streptococcus abscess of the arm. The child had not shown clinical evidence of cerebral hemorrhage, but the autopsy was unfortunately limited to an exploration of the region of the cerebellomedullary angle (see introduction) in which evidence of intracranial hemorrhage was not found. The icterus index of the spinal fluid at death was less than 1.

The duration of xanthochromia in premature infants, as indicated by table 5, appears to be longer than in the case of full-term infants. With respect to the latter, Roberts[41] stated: "The pigment persists at least until the ninth day and is cleared by the fourth week."

Of the eight cases of table 5 in which lumbar puncture was done during the first day of life, all the fluids showed xanthochromia, the average icterus index being less than 1. The icterus index was 2 in one case; 1 in two cases, and less than 1 in five cases. The series is small, but as far as the presence of xanthochromia during the first twenty-four hours of life is concerned, the results are in agreement with those of Roberts,[13] who found xanthochromia constantly present in a series of more than 300 new-born infants, in most of whom punctures were performed during the first twenty-four hours of life. Levinson[18] found twelve colorless fluids in the seventy-two clear fluids of his series of new-born infants, also in whom punctures were performed during the first twenty-four hours of life. Most of the infants of this series were born at full term. It is not impossible that the faint degree of xanthochromia in the twelve colorless fluids of Levinson's series may have escaped notice if the fluids were examined in artificial light, or if less than 1 cc. of fluid was examined. Dr. Levinson, in reading this manuscript, has accepted this as a valid suggestion with regard to his work.

40. Since the series was completed and this manuscript prepared, a water-clear, colorless spinal fluid was obtained from a premature infant, aged 35 days.

41. Roberts, M. H.: Physiological Pigmentation of the New-Born, J. M. A. Georgia **15**:4 (Jan.) 1926.

An icterus index of 4 occurred in three spinal fluids of this series. Two of the patients died, and cerebral hemorrhage was found at autopsy. In the third case, cerebral hemorrhage was suspected clinically, but the patient survived. Icterus indexes of 3 or less were not uncommon, regardless of the clinical diagnosis.

The highest icterus index recorded among the cases in table 5 was 11. This occurred in the spinal fluid of a normally delivered white male infant of thirty-four weeks' gestation. The patient was intensely jaundiced at the age of 8 days, when he was admitted to the Premature Infant Station, and weighed 1,820 Gm. Lumbar puncture at that time yielded a clear yellow fluid which had an icterus index of 11, gave a negative benzidine test, and contained only two red blood cells per cubic millimeter. At the age of 12 days, the patient was somewhat less jaundiced. The icterus index of the cerebrospinal fluid at that time was 5. Somewhat later it was noticed that the child's head was increasing in size, and that the sutures were becoming widely separated. The hydrocephalus slowly increased, and at the age of 23 days, lumbar puncture yielded a clear yellow fluid having an icterus index of 2. The child was somewhat jaundiced at that time. The next day he died, and permission for necropsy could not be obtained. Wassermann tests on both parents just previous to the admission of the child to the hospital were negative. It seemed highly probable that the child had hydrocephalus as a result of a cerebral hemorrhage, to which the high icterus index of the spinal fluid and the jaundice may also have been due.

Table 5 indicates that the icterus index is not greatest at birth but that it gradually increases, attaining a maximum during the second week of life (fig. 6). From then on, the icterus index gradually decreases to 0. This is true whether or not cerebral hemorrhage was present at birth, but the height attained by the icterus index in any given case is greater if cerebral hemorrhage has been present.

The relationship between the age of the infant and the icterus index of the cerebrospinal fluid is not absolute. An icterus index of less than 1 may be found at any age during which xanthochromia is present. An icterus index exceeding 1, however, was observed only once during the first twenty-four hours of life. The icterus index in this case was 2 and occurred in a female premature infant who weighed 2,005 Gm., and who died at the age of 17 hours from congenital malformations of the heart. Evidence of intracranial hemorrhage was not found at necropsy.

The fact that the icterus index of the cerebrospinal fluid is usually highest during the second and third weeks of life is interesting in that it implies a relationship to icterus neonatorum, which, when it occurs, is usually present at that time. This will be discussed under the consideration of the relationship of bilirubinemia and clinical jaundice to xanthochromia.

RELATIONSHIP OF THE ICTERUS INDEX OF THE CEREBROSPINAL FLUID TO THE PANDY TEST

In clear yellow cerebrospinal fluids giving a negative benzidine reaction and having an icterus index of 4 or less, the Pandy test was negative as often as it was positive. In these cases its presence and intensity seemed independent of the degree of xanthochromia. The Pandy test was two plus in the one instance in which the icterus index was 5, and was four plus in the single case in which the icterus index was 11.

THE VAN DEN BERGH REACTION

A consideration of the van den Bergh reaction is introduced at this point because in the discussion to follow on the origin and nature of the

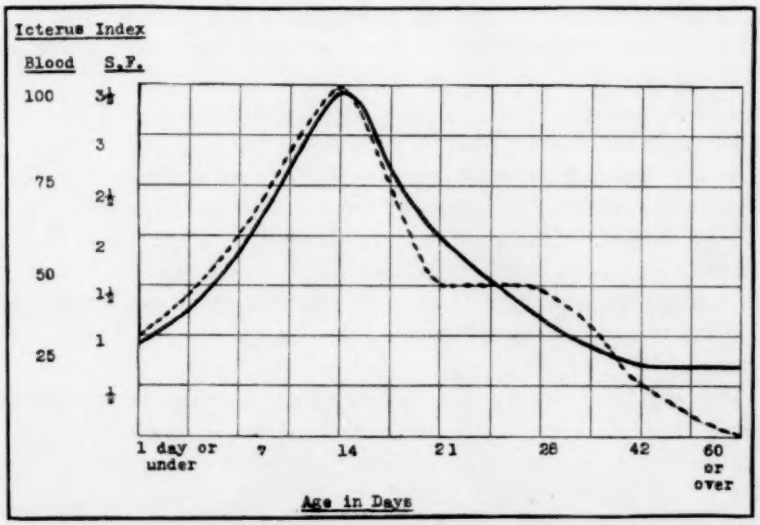

Fig. 6.—The relationship between the icterus index of the blood serum and of the cerebrospinal fluid and the age of the premature infant. The broken line indicates the spinal fluid and the solid line, the blood serum.

xanthochromia of cerebrospinal fluid, frequent reference will be made to this chemical reaction.

The van den Bergh reaction is the application of the diazo reaction of Ehrlich [42] to human blood serum and, in this study, to cerebrospinal fluid. The principle of the reaction depends on the fact that if a small amount of a diazonium salt in acid solution is added to an alcoholic solution of bilirubin, a reaction takes place with the development of a specific azo dye, "azo bilirubin." This dye was isolated and studied chemically

42. Ehrlich, P.: Ueber eine neue Harnprobe, Charité-ann. **8**:140, 1883.

and spectroscopically by Pröscher [43] in 1900, and by Orndorff and Teeple [44] in 1904. Van den Bergh and Snapper [45] studied Ehrlich's reaction on the blood serum with the result that this reaction, as applied to blood serum, became known as "the van den Bergh reaction."

Hemoglobin, hemosiderin, biliverdin, urobilin and the lipochromes do not give the van den Bergh reaction. A solution of pure bilirubin in alcohol as dilute as 1 : 1,500,000 will give a positive test. The normal concentration of bilirubin in the blood serum varies between 1 : 1,000,000 and 1 : 400,000. Above this concentration, jaundice will appear. Bilirubin appears in the urine when the concentration in the blood serum is about 1 : 50,000.

Van den Bergh was the first to observe that in some cases of jaundice it is unnecessary to bring the bilirubin into alcoholic solution before adding the diazo reagent, but that the presence of a positive reaction, as evidenced by the formation of the azo dye, may sometimes be obtained by adding diazo reagent directly to the icteric serum. This is known as the "direct van den Bergh reaction," and was believed to occur when the bilirubin was due to biliary obstruction.

By the "indirect van den Bergh reaction" is meant the appearance of a positive test after the proteins of the blood serum have been precipitated by alcohol. This reaction was thought to occur when the bilirubinemia was secondary to hemolysis. With either reaction, if the color does not appear within thirty seconds after the diazo reagent is added or if it appears late and deepens only slowly, the reaction is called "delayed."

The term "biphasic reaction" means that a color appears at once, and after a short time rapidly deepens. This term is avoided by some [46] because even in a prompt immediate reaction the maximum depth of color is not often attained before one or two minutes have elapsed. While this is true in general, there were a few instances in which, following a prompt immediate reaction, after a delay of several minutes there was a striking deepening of the color. For describing these reactions, we have found the term "biphasic" convenient.

Van den Bergh believed that the different types of reactions were probably due to the fact that different kinds of bilirubin were present.

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43. Pröscher, F.: Ueber Acetophenonazobilirubin, Ztschr. f. physiol. Chem. **29**:411, 1900.

44. Orndorff, W. R., and Teeple, J. L.: On Bilirubin, the Red Coloring-Matter of the Bile, Beitr. z. wissensch. Med. u. Chem., Festschr. f. Salkowski **23**:305, 1904.

45. Van den Bergh, A. A. H., and Snapper, J.: Die Farbstoff des Blutserums, Deutsches Arch. f. klin. Med. **110**:540, 1913.

46. Hall, W. W.: The Van den Bergh Reaction for Serum Bilirubin, with Notes on the Interpretation and Technique, J. Lab. & Clin. Med. **12**:529 (March) 1927.

For the purposes of this discussion it is sufficient to say that a positive van den Bergh reaction of any type is considered as evidence of the presence of bilirubin. A negative indirect van den Bergh reaction is considered as ruling out the presence of bilirubin. For a complete discussion of the van den Bergh reactions, reference may be made to the reviews of van den Bergh [47] and McNee.[48]

TECHNIC OF THE VAN DEN BERGH REACTION

Complete details of the procedure are omitted here because of lack of space. They may be found on reference to the works of van den Bergh [47] and McNee.[48]

Ehrlich's diazo reagent is prepared by mixing two solutions, 25 cc. of solution A and 0.75 cc. of solution B just prior to performing the test. Solution A is a 0.1 per cent solution of sulphanilic acid in a 1.5 per cent solution of hydrochloric acid. Solution B is a 0.5 per cent aqueous solution of sodium nitrite.

To perform the direct van den Bergh reaction, 0.5 cc. of the reagent is added to 0.75 or 0.5 cc. of spinal fluid. If the reaction is positive, a lavender color appears which, in case of a prompt immediate reaction, becomes a maximal deep violet in from ten to thirty seconds. A delayed reaction begins in from one half to fifteen minutes. Direct reactions were considered negative if color did not appear during one hour.

The indirect reaction is obtained by precipitating the spinal fluid proteins with twice the volume of 95 per cent alcohol. The solution is centrifugalized and to the supernatant fluid is added, in such a way as to form a layer, one fourth its volume of the diazo reagent. A violet red color appears in the presence of bilirubin.

THE VAN DEN BERGH REACTION OF CEREBROSPINAL FLUID AND ITS RELATIONSHIP TO THE ICTERUS INDEX

The indirect van den Bergh test was applied to forty-six of the yellow spinal fluids in table 5, and the direct test to forty-two. I have never observed a positive van den Bergh reaction in a colorless fluid, and I have never observed a positive direct reaction in blood serum or in spinal fluid when the indirect reaction was not also positive.

The indirect van den Bergh reaction was negative in twenty-three cases, or 50 per cent. The significance of this is that one half of the yellow spinal fluids of premature infants contain a yellow pigment which is due neither to the presence of hemoglobin in solution, that is, hemolysis, nor to the presence of bilirubin. This is not in accord with the observations of Roberts,[41] who found bilirubin regularly present, as attested by a positive van den Bergh reaction, in the cerebrospinal fluid of new-born infants. My observations are in accord with those of Levinson,[18] who stated that in sixty-eight yellow cerebrospinal fluids of his series both the benzidine and the van den Bergh reactions were

47. Van den Bergh, A. A. H.: Der Gallenfarbstoff im Blute, Leyden, S. C. van Doesburgh, 1918.

48. McNee, J. W.: Jaundice: A Review of Recent Work, Quart. J. Med. **16**:390 (July) 1923.

negative.) Levinson stated, and I agree with him, that the color may be due to the presence of an intermediary blood compound which gives a positive test for neither hemoglobin nor bilirubin. The fact that Roberts obtained a positive van den Bergh reaction in every one of his yellow fluids may perhaps be explained by the possibility that his process of concentrating the yellow fluids converted this presumptive intermediary form into bilirubin.

The results of the van den Bergh reactions of this series and their relationships to the icterus index are summarized in table 6. This table illustrates clearly that the van den Bergh reaction is not dependent on

TABLE 6.—*Comparative van den Bergh Reactions and Icterus Indexes of Cerebrospinal Fluid*

	Indirect van den Bergh			Direct van den Bergh		
Type of Reaction	Total Cases	Icterus Index	No. of Cases	Total Cases	Icterus Index	No. of Cases
Negative	23	< 1	12	35	< 1	15
		1	7		1	9
		2	1		2	3
		3	3		3	5
					4	2
					11	1
Faint delayed positive	6	< 1	1	3		
		1	4		3	3
		3	1			
Moderate delayed positive	0	..	..	2	3	1
					4	1
Faint immediate positive	7	2	4	1	2	1
		3	2			
		4	1			
Moderate immediate positive	8	< 1	1	0		
		2	1			
		3	4			
		4	2			
Strong immediate positive	2	5	1	0		
		11	1			

A definite biphasic direct reaction occurred in one case; icterus index 5.

the icterus index of the fluid, though in general, fluids with the higher icterus indexes give the stronger van den Bergh reactions. This independence of an absolute relationship between the icterus index and the van den Bergh reactions of spinal fluid seems rather definite additional evidence that even in those cases in which the van den Bergh reaction is positive there may also be present in the yellow fluid a pigment which does not give a van den Bergh reaction. That this yellow pigment may possibly be a precursor of bilirubin is suggested by the fact that while xanthochromia may or may not be accompanied by a positive van den Bergh reaction, in patients on whom repeated punctures have been performed a positive van den Bergh reaction almost invariably develops.

In the blood serum of premature infants, as in the spinal fluid, there may often be a marked disproportion between the height of the icterus

index and the intensity of the van den Bergh reaction. For example, a blood with an icterus index of 72 may give a van den Bergh reaction of the same character and intensity as a blood with an icterus index of 26. This confirms for premature infants van den Bergh's observation [47] with regard to adults, that the yellow color of the skin (which the icterus index reflects to a large extent) is not a reliable evidence of the degree of bilirubinemia, and leads to the same suggestion for blood serum as for spinal fluid, namely, that a yellow pigment may be present, often in relatively large amounts, which gives neither a van den Bergh nor a benzidine reaction, and therefore is presumably neither bilirubin nor hemoglobin. It is not improbable that in the blood, as in the spinal fluid, this substance is an intermediate product formed during the conversion of hemoglobin into bilirubin. The frequency with which jaundice occurs in premature infants is evidence of the activity with which bilirubin is elaborated in their metabolism.

Schnitzler [49] reported a yellow spinal fluid in a patient with carcinoma involving the vertebral column. Since the chemical tests on the fluid were negative for hemoglobin, bile pigment and urobilin, he suggested that the pigment might be due to lutein, but he did not make analyses for that substance.

Clarke and Lansdown [50] described a case of xanthochromia in a patient with a tumor of the spinal cord, and stated that the color was due to lutein. They did not give evidence to support this statement other than that the fluid was yellow.

At present I have little to say regarding the nature of the yellow pigment in the spinal fluids of this series which gave neither a van den Bergh nor a benzidine reaction. The pigment does not give the reactions of the lipochrome group. Since the pigment in a limited series of cases has given a positive test for iron, it is possible that the pigment is hemosiderin, or perhaps a closely related, more soluble compound, formed by the action of the mesothelial cells lining the subarachnoid spaces on red blood cells or free hemoglobin.

The direct van den Bergh reaction was negative in thirty-five of forty-two yellow cerebrospinal fluids, or in 83 per cent of the cases. This reaction, like the indirect reaction, seems to be independent of the icterus index, although it is interesting to note that positive direct reactions were not obtained in fluids having an icterus index of less than 2. A positive delayed reaction occurred six times. Three of these patients came to necropsy and showed cerebral hemorrhage; another died and

49. Schnitzler, J. G.: Klinische Beiträge zur Kentniss der mit Muskelatrophien verlaufenden Formen von multiper Sklerose und chronischer Myelite, Ztschr. f. d. ges. Neurol. u. Psychiat. **12**:310, 1912.

50. Clarke, J. M., and Lansdown, R. G. P.: Intramedullary Tumor of Spinal Cord, Brit. M. J. **1**:1009 (May) 1914.

permission for necropsy could not be obtained. The two remaining patients, who showed strong clinical evidence of cerebral hemorrhage, survived.

Three other instances of water-clear spinal fluids which gave negative benzidine reactions and positive delayed direct van den Bergh reactions were observed in this series but were not included in table 6, because at the time they occurred the icterus index of cerebrospinal fluid was not being determined. Two of these cases showed a relatively small degree of intracranial hemorrhage at necropsy, and the third showed only kern icterus. A positive direct van den Bergh reaction in water-clear cerebrospinal fluid giving a negative benzidine test is strongly suggestive of previous intracranial hemorrhage.

A well marked biphasic reaction was observed only once in the cerebrospinal fluids of this series. This occurred in a patient who undoubtedly had an intracranial hemorrhage. Biphasic reactions occurred several times in the blood serum of premature infants, but a consideration of these cases is not necessary in this discussion.

A positive direct van den Bergh reaction was noted only once in the eight patients of table 5 who were 1 day of age or less. In this case the indirect reaction was moderately strong and immediately positive. The direct reaction was delayed and faint. This occurred in a premature infant weighing 1,380 Gm., whose condition was diagnosed clinically as intracranial hemorrhage. The child died shortly after the puncture, and permission for necropsy could not be obtained.

ORIGIN OF BILIRUBIN OCCURRING IN CEREBROSPINAL FLUID AND RELATIONSHIP OF VAN DEN BERGH REACTION AND ICTERUS INDEX TO PREVIOUS CEREBRAL HEMORRHAGE

The fact that bilirubin or its isomere, hematoidin, may be formed in any tissue of the body whenever hemoglobin is liberated by hemorrhage is well established.[51] Hooper and Whipple [52] showed that hemoglobin, either in the crystalline form or as whole blood, may be converted into bile pigment when introduced into the pleural or peritoneal cavities. This transformation takes place so rapidly that it may be detected by qualitative tests after eight hours, and the amount may often be estimated quantitatively within twenty-four hours. Hooper and Whipple believed that the transformation is brought about by the activity of the mesothelial cells lining these cavities.

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51. Whipple, G. H.: Origin and Significance of the Constituents of the Bile, Physiol Rev. **2**:440 (July) 1922.

52. Hooper, C. W., and Whipple, G. H.: A Rapid Change of Hemoglobin to Bile Pigment in the Pleural and Peritoneal Cavities, J. Exper. Med. **23**:137, 1916.

By analogy it might reasonably be suspected that the same transformation would be brought about under similar circumstances in the cerebrospinal fluid system, which is also a mesothelial lined cavity, except for the ependyma. A review of the literature on xanthochromia reveals that this has been suggested previously.

Experimental work in this direction was done by Leschke [28] in 1921. His experiments were made in the course of the intraspinal treatment of syphilis by means of arsphenaminized serum. In four cases, Leschke injected intraspinally a suspension of the patient's washed red blood cells in the patient's serum. In from three to four days the fluid showed a light yellow color, and in a few more days gave a positive van den Bergh reaction for bilirubin. Leschke concluded that the transformation of the hemoglobin into bilirubin took place as the result of ferments produced by the vital activity of the endothelial cells of the central nervous system, since this transformation did not occur in a control specimen of cells and serum placed in an incubator.

Leschke attempted to demonstrate the presence of ferments in the spinal fluid by withdrawing some of the yellow spinal fluid two days after the intraspinal injection of the red blood cells. He centrifugalized this fluid and to half of the supernatant fluid added washed red blood cells. The other half was used as a control. After incubation, the presence of a substance able to change hemoglobin into bilirubin was demonstrated by a greater increase of the bilirubin content in the tube containing the red blood cells than in the control tube. While the transformation of hemoglobin into bilirubin undoubtedly occurs in the spinal canal, Rich and Bumstead [53] do not accept Leschke's experiments as positive evidence that it is due to an enzyme.

I have observed the disappearance of red blood cells and a positive benzidine reaction and the development of a positive van den Bergh reaction in vivo in the spinal fluid of an adult within forty-eight hours after a previously clear spinal fluid was made bloody by accidental manipulation of the needle during a spinal puncture.

Of the fifteen patients in table 6 from whom twenty-three yellow spinal fluids which gave a negative van den Bergh reaction were obtained, seven came to necropsy and none of these showed evidence of previous cerebral hemorrhage. The icterus indexes in these cases were 3, 2 and 1 in each of three cases, and less than 1 in each of four cases. In three other cases, two of which were suspected of cerebral hemorrhage, necropsies could not be obtained. Five patients, one of whom was suspected of cerebral hemorrhage, were discharged alive.

53. Rich, A. R., and Bumstead, J. H.: Bile Pigment from Hemoglobin. Bull. Johns Hopkins Hosp. **36**:436, 1925.

Of the nineteen patients of table 6 from whom twenty-four spinal fluids which gave a positive van den Bergh reaction were obtained, five came to necropsy and four of these showed subarachnoid hemorrhage. In only one case (case 5 of table 4) was the hemorrhage considered large enough and so located as to have been the possible cause of death. In the fifth case, only pneumonia was found. In the four cases that showed intracranial hemorrhage, the icterus indexes were 4, 4, 3 and 3. The icterus index of the spinal fluid of the patient with pneumonia was 1. Postmortem examinations were not made in three cases, two of which had been diagnosed as intracranial hemorrhage. Of the ten

TABLE 7.—*Multiple Spinal Punctures in Suspected Cases of Cerebral Hemorrhage*

Case	Age in Days	Red Blood Cells per C.Mm.	Benzidine Test	Icterus Index	Van den Bergh Reaction	
					Indirect	Direct
1	⅛	66,800	+	4	Moderate immediate +	Faint delayed +
	3	48,800	+	7	Moderate immediate +	Moderate delayed +
2	⅛	82,000	+	2	Moderate delayed +	0
	11	540	+	5	Faint delayed +	0
	107	0	0	0	0	0
3	1/48	8,500	+	< 1	0	0
	1⅛	80,000	+	10	Faint immediate +	0
4	1	3,600	+	3	Moderate delayed +	Moderate delayed +
	10	20	0	4	Faint immediate +	0
5	⅛	2,880	+	1	0	0
	10	100	0	1.5	Faint immediate +	0
	16	0	0	2.5	Faint immediate +	Moderate delayed +
	38	0	0	Trace	0	0
6	1	2,800	+	1	Not done	Not done
	8	2,380	+	1	0	0
	25	50	0	1	0	0
7	½	4	0	1	0	0
	3	15	0	2	0	0
	6	2	0	3	Moderate immediate +	0
	22	1	0	2.5	Moderate immediate +	Faint delayed +
8	1⅛	0	0	< 1	0	0
	7	0	0	< 1	0	0
	9	2	0	< 1	0	0

surviving patients, signs of intracranial hemorrhage had been present in six.

The evidence presented in the two foregoing paragraphs is suggestive that when cerebral hemorrhage has occurred at birth the icterus index will be higher and the van den Bergh reactions more often positive and more strongly positive than in those cases in which cerebral hemorrhage had not occurred. The condition found at any given puncture, assuming that a faulty tap has not been made, will depend largely on the interval that has elapsed since the time of the hemorrhage.

Further evidence indicating the conversion of hemoglobin into bilirubin is given by a study of the results of multiple punctures in those patients from whom bloody spinal fluid was obtained at the time of the first puncture. These cases, together with one or two others, are

recorded in table 7. When red blood cells were present in the fluid, the icterus index was determined on a centrifugalized specimen. All the cases in table 7 presented some of the symptoms of intracranial hemorrhage.

CASE 1.—At necropsy, this infant showed a thin layer of subarachnoid hemorrhage covering the upper surface of the cerebellum.

CASE 2.—In some respects, this case was the most remarkable of the series. This child was the premature infant son of a primipara delivered in a normal manner after what was said to be six months' gestation but which was undoubtedly longer. The weight at birth was 1,415 Gm. The patient was first seen at the age of 3 hours, at which time he was having repeated attacks of cyanosis and redness, sometimes as often as once every minute. In my experience with premature infants, such attacks of alternating cyanosis and redness have been practically pathognomonic of subtentorial intracranial hemorrhage.

Because of the severity and frequency of the attacks of cyanosis, a fatal prognosis was given. Lumbar puncture was done at the age of 4 hours, and about 3 cc. of grossly bloody fluid withdrawn. The cyanotic attacks ceased almost immediately after the puncture. A few attacks occurred the following day, but several attempts to obtain fluid from the spinal canal were unsuccessful. During the week there were a few more attacks of cyanosis, and at the age of 11 days another lumbar puncture was performed. The fluid was deep yellow (icterus index, 5) and contained 540 red blood cells per cubic millimeter, two thirds of which were crenated. The child's further progress was uneventful, and he was discharged at the age of 42 days. At the age of 107 days, he was readmitted for observation. He then weighed 2,525 Gm., and physical examination did not show any evidence of abnormality. Spinal puncture revealed normal fluid. When last seen at the return clinic at the age of 9 months, the infant was apparently normal.

CASE 3.—A premature male infant of about six months' gestation, delivered spontaneously, weighed 975 Gm. at birth. When received at the Premature Infant Station one-half hour afterward, the child was moaning constantly. The anterior fontanel was tense, slightly bulging and pulsating. This was one of the three cases in our series in which a bulging fontanel was observed in intracranial hemorrhage and the only time a fontanel was felt to pulsate. The lips and finger tips were slightly cyanotic at times. A diagnosis of intracranial hemorrhage was obvious, and a spinal puncture was done immediately. One cubic centimeter of slightly bloody fluid containing 8,500 red blood cells per cubic millimeter, all of which were crenated, was withdrawn. Following this the fontanel became depressed, the cyanosis disappeared and the moaning also stopped for a short time. During the night the child did fairly well, but the next morning the cyanotic attacks reccured, the child seemed to have difficulty in breathing on account of mucus in his throat, and died at the age of 28 hours. Spinal puncture was done immediately after death and grossly bloody fluid containing 80,000 red blood cells per cubic millimeter was obtained.

At necropsy, the cortex of the brain was free from hemorrhage. Slightly yellow cerebrospinal fluid could be seen in the subarachnoid spaces. There was, however, a rather marked degree of internal hydrocephalus owing to the presence of a large blood clot which formed a cast of the ventricular system and cisterna magna, complete to such minute anatomic details as the prolongations of the third ventricle into the optic and infundibular recesses and the prolongations of the

fourth ventricle toward the lateral foramina. Because of the uniform color and consistency of the clot, it is highly probable that its formation occurred during life.

CASE 4.—This infant also showed intracranial hemorrhage at necropsy. This case has been discussed previously as case 5 of table 4.

CASE 5.—In a colored female premature infant who weighed 1,750 Gm. at birth, periodic attacks of cyanosis could be detected, in spite of the child's naturally dark skin. The child was discharged at the age of 38 days, weighing 2,270 Gm. and apparently normal physically. The spinal fluid at that time had a scarcely perceptible trace of yellow.

CASE 6.—This infant had intermittent attacks of cyanosis which persisted for a few days after birth. The first spinal puncture gave about the same results as that in case 5. The child died at the age of 25 days. Unfortunately, permission for necropsy could not be obtained. The facts that the color index of the spinal fluid did not change during that period and that a positive van den Bergh reaction did not appear leads to the suspicion that the diagnosis of cerebral hemorrhage at birth was incorrect.

CASE 7.—A premature male infant of about thirty weeks' gestation, who weighed 1,520 Gm. at birth, was one of twins whose delivery was normal. For a period of several days after birth the child had intermittent attacks of cyanosis with occasional redness of the skin in the intervals between the attacks. Punctures done at three day intervals showed the development of a progressive increase in the icterus index and the development of a positive van den Bergh reaction. The clinical diagnosis was cerebral hemorrhage. The child had a difficult convalescence, chiefly because of gastro-intestinal disturbances, but when discharged at the age of 1 month was apparently normal except for his small size.

CASE 8.—Although this case was not an instance of cerebral hemorrhage, it is included here because of its interest when compared with the other cases of the table. The patient was a premature male infant of about thirty-seven weeks' gestation who weighed 1,935 Gm. at birth. Delivery was made by the application of low forceps. Because of attacks of cyanosis, at first intermittent and later continuous, the consensus was that the child had a cerebral hemorrhage, and when the first spinal puncture at the age of 28 hours revealed an essentially normal fluid the hemorrhage was believed to be subpial. However, when repeated punctures on the seventh and ninth day did not show a change in the spinal fluid, the diagnosis of cerebral hemorrhage was considered not substantiated. A roentgenogram was taken to rule out, as far as possible, the other cardinal causes of cyanosis in the new-born, namely, atelectasis, congenital heart disease and enlarged thymus. The roentgenographic diagnosis was congenital heart disease and enlargement of the thymus gland. The child died that night and at necropsy an enlarged thymus was found and a heart presenting numerous congenital anomalies.

Examination of table 7 shows that every case of intracranial hemorrhage coming to autopsy and every case except one in which intracranial hemorrhage was diagnosed clinically was accompanied by a progressive increase in the icterus index of the cerebrospinal fluid, up to a certain point, and the development of a positive van den Bergh reaction. In most cases this paralleled the disappearance of the red blood cells. Several additional case reports paralleling cases 1, 2, 5 and 7 could be

included here but are omitted for the sake of brevity. It is interesting to note that in several of these cases lumbar puncture, in addition to being an aid in diagnosis, appeared to have decided therapeutic value in relieving the symptoms of intracranial hemorrhage. Cases of intracranial hemorrhage of this series in which the infants have survived thus far (from two months to one year) have not shown any evidence of permanent injury due to cerebral hemorrhage at birth.

It is my opinion that every patient with cerebral hemorrhage, except those in whom the hemorrhage is purely interstitial, if punctures are performed at frequent enough intervals (for example, every third day), will show a progressive increase in the icterus index of the cerebrospinal fluid and the development of a positive van den Bergh reaction. This may also occur in spinal fluids in which gross hemorrhage has not occurred, but the duration and intensity of the xanthochromia and the van den Bergh reactions will be greater in infants with hemorrhage and will vary with the extent of the hemorrhage. Frequent punctures are necessary to detect these changes, because parallel with the breaking down of the hemoglobin in the spinal fluid there is a constant absorption of the hemoglobin and its decomposition products.

The intermediate territory between microscopic and gross cerebral hemorrhage is possibly represented by those cases in which the icterus index of the spinal fluid attains a maximum of 3. Probably under certain circumstances, such as kern icterus, a form of icterus distinctly affecting the central nervous system, the icterus index of the cerebrospinal fluid may be as high or higher without hemorrhage. Such a relationship between hemorrhage and the indirect van den Bergh reaction cannot be suggested here in the absence of exact quantitative studies on the bilirubin content of the cerebrospinal fluid. However, a positive direct van den Bergh reaction in this series, except for one case of kern icterus, has occurred only in those cases in which cerebral hemorrhage was found at autopsy or was strongly suspected clinically.

XANTHOCHROMIA DURING THE FIRST TWENTY-FOUR HOURS OF LIFE

Gibb [54] and Seitz [55] each reported a case of intracranial hemorrhage which occurred in utero before labor began, the most likely cause of which was trauma to the abdomen of the mother during pregnancy. Osler [56] also reported a case of antenatal cerebral hemorrhage apparently

54. Gibb, C. D.: Congenital Hemiplegia in a Stillborn Child in a Case of Placental and Funis Presentation, Lancet **2**:497, 1858. This is the case quoted by Cotard, J.: Étude sur l'Atrophie Cérébrale, Paris, 1868.

55. Seitz, L.: Ueber die durch intrauterine Gehirnhämorrhagien entstandenen Gehirndefecte und die Encephalitis, Arch. f. Gynäk. **83**:701, 1907.

56. Osler, W.: Case of Cerebral Hemorrhage in a Foetus, Teratologia **2**:13, 1895.

as a result of typhoid fever during the mother's pregnancy. Seitz expressed the opinion that porencephaly is probably the result of antenatal cerebral hemorrhage.

Although it is certain that cerebral hemorrhage will result in xanthochromia, it is highly improbable that the invariable occurrence of xanthochromia during the first day or the first hours of life can be explained on the basis of antenatal cerebral hemorrhage. The possibility that a yellow spinal fluid is secreted by the choroid plexus during antenatal life must be considered. In the series here under discussion this could not be put to the test, because there was no opportunity to perform lumbar punctures on infants delivered by cesarean section before labor began.

A plausible explanation of xanthochromia is that it is due to the transudation of blood serum or plasma and its accompanying pigments through congested cerebral vessels during the period of labor. Sprunt and Walker [31] suggested transudation of plasma as an explanation of the xanthochromia occurring in obstruction to the circulation of the cerebrospinal fluid with formation of a culdesac, and Cushing [57] expressed the belief that transudation of serum may be the explanation of xanthochromia occurring in persons with tumors of the central nervous system.

During the passage of the fetus through the birth canal, the portion first delivered, usually the head, is relieved from the direct pressure of the uterine contractions. The compression of the undelivered portion of the child by the contracting uterus causes intense intracranial congestion. The skull of the new-born infant, as Cushing [58] pointed out, is well fitted to withstand pressure by virtue of the fontanels, the easily separated sutures and the incompletely medullated, soft, yielding brain structures within.

One important structure of the new-born, however, and particularly the new-born premature infant, is unable to withstand pressure as well as might be thought desirable in the light of the present knowledge. That structure is the blood-vascular system, particularly the smaller vessels of the pia, the subarachnoid spaces, the cortex and the ependyma. Ylppö,[59] by means of a suction apparatus applied to the skin, has shown quantitatively the inability of the smaller vessels to withstand any marked degree of increased intravascular pressure. For example, in premature infants weighing under 1,000 Gm., hemorrhage is produced in the

57. Cushing, Harvey, and Ayer, J. B.: Xanthochromia and Increased Protein Content in the Cerebrospinal Fluid above Tumors of the Cauda Equina, Arch. Neurol. & Psychiat. **10**:167 (Aug.) 1923.

58. Cushing, Harvey: Intracranial Hemorrhage of the New-Born, Am. J. M. Sc. **130**:563, 1905.

59. Ylppö, A.: Zum Entstehungsmechanismus der Blutungen beim Frühgeburten und Neugeborenen, Ztschr. f. Kinderh. **38**:32, 1924.

cutaneous vessels by subjecting them to a suction pressure of 150 mm. of mercury. The ease with which the vessels rupture decreases rapidly as the size of the child and its nearness to term increases. In infants weighing up to 1,500 Gm., the vessels are ruptured by a pressure of 250 mm. of mercury; in those weighing up to 2,000 Gm., by 310 mm. of mercury.

When one associates these observations, as Ylppö did, with those of Schatz,[60] who showed that at the height of contraction the intra-uterine pressure not infrequently rises to 250 mm. of mercury in excess of atmospheric pressure and may rise higher, it is not a cause for wonder that hemorrhages occur so frequently in premature infants, as often as in 90 per cent of Ylppö's [10] cases in which the infants weighed under 1,000 Gm. Previous to the observations of Ylppö, Schwartz [61] called attention to the work of Schatz and pointed out that the difference between the intra-uterine pressure on the undelivered portion of the infant and the atmospheric pressure on the presenting part had the effect of a suction mechanism on the presenting part, causing congestion and possibly hemorrhage.

With the intracranial hemorrhages, as might be expected, hemorrhages are found in other parts of the body. Of particular interest are those of the eyegrounds, because of the close relationship of the ophthalmic to the cerebral vessels. Paul [62] found hemorrhages in the eyegrounds of 40 per cent of premature infants. Stumpf and von Sicherer [63] reported retinal hemorrhages in 32 per cent of new-born premature infants as compared with 18.7 per cent of retinal hemorrhages in full term infants.

The foregoing facts indicating the congestion of the vessels of the central nervous system during labor strongly suggest that some transudation might take place during that time from these vessels into the spinal fluid. How small an amount of transudate would be required to cause a significant degree of xanthochromia is indicated by the following study: Of eight premature infants who died at the age of 1 day or less, the average icterus index of the heart's blood withdrawn immediately after death was 26. The largest amount of fluid that could be withdrawn from the spinal canal of infants of the average weight of these eight, 1,200 Gm., was about 6 cc. It would be fair to assume that at least

60. Schatz, F.: Beiträge zur physiologischen Geburtskunde, Arch. f. Gynäk. **3**:58, 1872.

61. Schwartz, P.: Ansaugungsblutungen im Gehirn Neugeborener, Ztschr. f. Kinderh. **29**:102, 1921.

62. Paul, quoted by Seitz, L.: Ueber die Genese intracranieller Blutungen bei Neugeborenen, Zentralbl. f. Gynäk. **36**:1 (Jan. 6) 1912.

63. Stumpf, M., and von Sicherer: Ueber Blutungen ins Auge bei Neugeborenen, Beitr. z. Geburtsh. u. Gynäk. **13**:408, 1909.

6 cc. more remained in the spinal fluid reservoir, making a total of 12 cc. Therefore, to dilute the spinal fluid so that the icterus index would be 1, the average icterus index of the spinal fluid of infants during the first day of life would require a transudation of slightly less than 2 cc. of fluid. This does not seem to be a large amount of transudate when one considers the pressure with which the cerebrospinal vessels of the child are distended during labor.

If transudation from the cerebrospinal vessels into the cerebrospinal fluid occurs during labor, as seems highly probable, other constituents of the blood besides pigments should be found in the spinal fluid in increased amounts. My evidence with respect to this is limited to the Pandy test for globulin. Thus, while the Pandy reaction has been negative in older infants whose spinal fluid had an icterus index as high as 4, in the spinal fluid of infants under 1 day of age the reaction is usually 1 plus or more. This speaks for a transudation of plasma protein as well as pigment, but the evidence on this point is inconclusive because of the paucity of cases.

The presence of red blood cells in macroscopic numbers in the cerebrospinal fluid of new-born premature infants, as well as of infants born at full term, is also to be explained, at least in part, by diapedesis of the red blood cells or rhexis (capillary hemorrhage) through the congested cerebrospinal vessels during labor. The liberation by hemolysis of the hemoglobin of these red blood cells with the subsequent conversion of the hemoglobin into bilirubin and probably other pigments is doubtless an important factor in prolonging the initial xanthochromia of these infants.

THE RELATIONSHIP BETWEEN ICTERUS AND XANTHOCHROMIA

It has been pointed out previously in this paper that the icterus index of cerebrospinal fluid is usually highest during the second week of life, and that this is interesting in that it implies a relationship to icterus neonatorum, which, when it occurs, is usually present at that time. While there is no doubt regarding the autochthonous production of bilirubin from hemoglobin in the cerebrospinal fluid system, there is considerable variation of opinion in the literature regarding the presence of bile pigment in the cerebrospinal fluid independent of local hemorrhage or transudation and secondary to bilirubinemia or icterus.

In five patients with severe jaundice, Mongour [64] did not find bile pigment in, or xanthochromia of, the cerebrospinal fluid.

64. Mongour, C.: Sur la teneur du liquide cephalorachidien en pigments biliares dans les ictères choluriques, Compt. rend. Soc. de biol. **57** (Part 2):397 (Nov. 12) 1904.

In three patients with severe jaundice of four, six and eight weeks' duration, respectively, Rotky [65] did not find bilirubin in the spinal fluid.

Bauer and Spiegal [66] and Obermayer and Popper [67] expressed the opinion that xanthochromia does not occur as a result of icterus, but they did not report any cases.

In his extensive monograph on cerebrospinal fluid, written in 1911, as a result of a review of the literature and some observations of his own, Mestrezat [7] stated that the cerebrospinal fluid is colored yellow in some cases of jaundice but not in all. He also stated that the principal pigments in the yellow spinal fluids occurring in jaundice are those of the bile but that other pigments may be present, notably urobilin.

Mella [68] reported six cases of jaundice accompanied by markedly yellow cerebrospinal fluid which when tested did not show bile pigments. Four of these occurred in syphilitic patients after treatment with arsphenamine; another occurred in a patient with arthritis who had received arsphenamine seven weeks previously, and the sixth occurred in a patient with carcinoma of the pancreas. When tested for bile, the urine gave strongly positive reactions in every case.

Naunyn [69] stated that in persons with jaundice the cerebrospinal fluid always contains bile pigment.

Levinson [5] wrote that in persons with jaundice the cerebrospinal fluid is yellow and when tested for bile gives a positive reaction.

Brogsitter and Krauss [70] expressed the belief that every long-standing case of severe jaundice is accompanied by the passage of bile pigment into the cerebrospinal fluid.

Müller [71] wrote that a yellow color of the cerebrospinal fluid regularly occurs in persons with intense jaundice.

Gilbert and Castaigne,[72] by employing the Gmelin and Pettenkoffer tests, demonstrated the presence of bile pigment in the spinal fluid in

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65. Rotky, H.: Untersuchung über die Durchlässigkeit der Meningen für chemische Stoffe, Ztschr. f. klin. Med. **75**:494, 1912.

66. Bauer, J., and Spiegal, E.: Ueber das Bilirubin im Blute und seine pharmakologische Beeinflusbarkeit, Deutsches Arch. f. klin. Med. **129**:17, 1919.

67. Obermayer, F., and Popper, H.: Ueber den Nachweis von Gallenfarbstoff und dessen klinische Bedeutung, Wien. med. Wchnschr. **60**:2591, 1910.

68. Mella, H.: Cerebrospinal Fluid in Jaundice, Arch. Neurol. and Psychiat. **8**:329 (Sept.) 1922.

69. Naunyn, B.: Ueber Ikterus und seine Beziehungen zu den Cholangien, Mitt. a. d. Grenzgeb. d. med. u. Chir. **31**:537, 1919.

70. Brogsitter, A. M., and Krauss, E.: Vergleichende chemische Analysen normaler und pathologischer Körperflüssigkeiten, Arch. f. klin. Med. **143**:297, 1924.

71. Müller, E.: Handbuch der Inneren Medizin—von Bergmann-Staehelin, ed. 2, Berlin, Julius Springer, 1925, vol. 5, p. 464.

72. Gilbert, A. A., and Castaigne, J.: Le liquide cephalorachidien dans la cholémie, Compt. rend. Soc. de biol. **57**:877, 1900.

three out of eighteen patients with jaundice. They observed that the passage of bile into the spinal fluid did not seem to depend altogether on the amount of bile in the patient's blood or on the condition of the kidneys.

Von Gündell and Jacobi [73] demonstrated the presence of bile pigment in six patients with jaundice by means of the van den Bergh reaction in three patients in whom yellow cerebrospinal fluid was present. Two of these cases occurred in patients with carcinoma, and in the third case the diagnosis was not stated. Hence there is the possibility, in the absence of direct evidence to the contrary, that the pigment was secondary to hemorrhage from metastases into the central nervous system. The authors concluded that the passage of bilirubin into the cerebrospinal fluid takes place with a blood bilirubin concentration of 1:40,000. There was not sufficient bilirubin in the spinal fluid to permit a quantitative determination in any case.

Schmorl [74] stated that while the spinal fluid in persons with severe icterus is regularly colored a faint yellow by bile, the ventricular fluid is regularly clear. In ten cases of icterus in adults, he found the ventricular fluid colorless in seven cases. In one case of eight months' standing, the ventricular fluid was pale yellow but did not give a reaction for bile pigment. In two cases the ventricular fluid was intensely yellow, due to bile pigment, and was a deeper yellow than the spinal fluid. From the results of necropsies on these patients, Schmorl concluded that in the presence of icterus bile pigment passes into the ventricular fluid only when the choroid plexus or ependyma of the ventricles is damaged.

Ducrot and Gautrelet [75] produced severe jaundice in dogs by ligation of the common bile duct and found neither xanthochromia nor bile present in the cerebrospinal fluid after from two to eight days. After ligating the external carotid arteries, they injected methyl violet into the internal carotid arteries. After fixation of the dye in the choroid plexus, which took about fifteen minutes, the spinal fluid became yellow and gave a positive reaction to Gmelin's test for bile. Little by little, as the methyl violet was eliminated from the choroid plexuses, the fluid became colorless and when tested did not show bile pigment. In two cases this took place within twenty-four hours of the injection of methyl violet.

73. Von Gündell, H., and Jacobi, I.: Ueber den Austausch von Bilirubin zwischen Blut und Liquor, Arch. f. klin. Med. **153**:215 (Dec.) 1926.

74. Schmorl, G.: Liquor Cerebrospinalis und Ventrikelflüssigkeit, Verhandl. d. deutsch. path. Gesellsch. **14**:228, 1910.

75. Ducrot, R., and Gautrelet, J.: Le liquide céphalo-rachidien au cours de l'ictère experimental, Compt. rend. Soc. de biol. **58**:160, 1905.

It thus appears, from the foregoing review of the literature, that bile pigment does not regularly appear in the spinal fluid even in the presence of intense jaundice. Its appearance presumably means the presence of another factor, possibly damage to the choroid plexus or the ependyma of the ventricles.

The problem of the relationship between icterus neonatorum and xanthochromia of the cerebrospinal fluid may be attacked from two principle angles: (1) the relationship between the icterus index of the blood and the icterus index of the cerebrospinal fluid, and (2) the relationship between the van den Bergh reactions of the blood serum and the van den Bergh reactions of the cerebrospinal fluid.

THE RELATIONSHIP OF THE ICTERUS INDEX OF THE BLOOD SERUM TO THE ICTERUS INDEX OF THE CEREBROSPINAL FLUID

In a general way, the relationship between the icterus index of the blood serum and the icterus index of the cerebrospinal fluid during the first weeks of life is summarized by figure 6. The materials from which these curves were plotted are the spinal fluids of table 5 and the icterus indexes of the blood serum of thirty-seven premature infants of various ages withdrawn from the heart immediately after death or from the superior longitudinal sinus during life, without regard to the clinical diagnosis.

The curves of figure 6 may also be taken to illustrate the relationship between the icterus index of the cerebrospinal fluid and the degree of clinical jaundice, which the icterus index of the blood serum represents rather accurately. This is particularly true in premature infants, in whom the facts that the skin is often much more red than in older infants, and that the sclerotics are frequently not easily seen make a diagnosis of a moderate degree of jaundice at times difficult. In children of the colored race, to which many of the patients of this series belong, the icterus index of the blood serum is particularly of great help in determining the degree of clinical jaundice.

Figure 6 indicates that during the first three weeks of life the icterus index of the cerebrospinal fluid closely parallels that of the blood serum. During the fourth week the icterus index of the cerebrospinal fluid remains at a plateau of 1½, from which it gradually descends to zero at about sixty days, and probably sometimes earlier. The icterus index of the blood serum during the fifth week of life descends to 15, at which level it subsequently remains. It is interesting to note that this level is at the threshold for the appearance of clinical jaundice in adults. In general, it was observed that premature infants have a higher threshold for the appearance of clinically recognizable jaundice throughout the early weeks of life than do adults. Roberts [41] made the same

observation in the case of full term infants, and a high icterus index was noted in the blood serum of three premature infants by Taylor.[76]

Figure 6 suggests that since the icterus index of the cerebrospinal fluid parallels the icterus index of the blood serum the former may be dependent on the latter, since the icterus index of the blood serum is always higher than that of the cerebrospinal fluid. In compiling the statistics of this series, however, I found it quite apparent that the higher icterus indexes of the cerebrospinal fluid were invariably, in the cases in which autopsy was performed (with the exception of one case of kern icterus), associated with some degree of grossly recognizable cerebral hemorrhage. It was also striking that the higher icterus indexes of the blood serum and clinically recognizable jaundice occurred much more frequently in patients with cerebral hemorrhage than in those not showing hemorrhage. This suggests that the degree and probably, in some cases, also the incidence of icterus neonatorum is influenced by the presence of cerebral hemorrhage, and to this, doubtless, should be added hemorrhage in any other portion of the body. In view of the fact, already discussed, that hemoglobin free in the cerebrospinal fluid or in any tissue of the body is converted into bilirubin, this is not surprising.

The conception of cerebral hemorrhage as a cause of icterus neonatorum is not new. In 1902, Skorim[77] reported a case of moderate jaundice in a living infant with definite clinical signs of intracranial hemorrhage, to which the jaundice was attributed. He also quoted a case, reported by Raudnitz in 1884, of severe jaundice in a premature infant in whom cerebral hemorrhage was discovered at autopsy. Raudnitz considered that the hemorrhage was the cause of the jaundice. More recently, the relationship between intracranial hemorrhage and jaundice was emphasized by Deluca.[78]

In the series of premature infants of this study, thirty-six on whom observations regarding icterus of the skin were recorded at the time of the various lumbar punctures came to necropsy. Of twenty-one who did not show evidence of cerebral hemorrhage, icterus was observed in seven, or 33 per cent; of the fifteen showing cerebral hemorrhage at necropsy, ten, or 66 per cent, also showed icterus.

According to Hess,[79] the so-called physiologic icterus of the new-born premature infant may appear within a few hours after birth and persist

76. Taylor, R.: Icterus Index in Children, Am. J. Dis. Child. **34**:989 (Dec.) 1927.

77. Skorim, B.: Ueber die verschiedenen Formen des Ikterus im Säuglingsalter, Jarhrb. f. Kinderh. **56**:176, 1902.

78. Deluca, F. A.: Contribución al estudio fisiopatogénico de la ictericia del recién nacido, Semana méd. **28**:635 (Nov. 10) 1921.

79. Hess, J. H.: Premature and Congenitally Diseased Infants, Philadelphia, Lea & Febiger, 1921, p. 286.

for several weeks. If the infants over 30 days of age and one who was stillborn are excluded from the foregoing series, the percentage of icterus in infants not showing evidence of cerebral hemorrhage rises to 36 per cent. It must be stated that of the patients in this series showing jaundice, one case each of death occurred from congenital syphilis, sepsis of the new-born and otitis media—any one of which is a sufficient explanation for the presence of jaundice. If from the series of infants showing cerebral hemorrhage one who was stillborn and one over 30 days of age are excluded, the percentage of cases showing jaundice rises to 77 per cent.

The foregoing observations, while incomplete, strongly suggest that cerebral hemorrhage not infrequently contributes to icterus neonatorum. In some cases, perhaps, the presence of a cerebral hemorrhage without clinical signs or even gross blood in the spinal fluid may be the explanation of what, for want of a proper understanding of its etiology, was called "physiologic" icterus neonatorum.

The impression gained from this work is that the pigmentation of the cerebrospinal fluid, except possibly in kern icterus or in other severe forms of jaundice, is unrelated to pigmentation of the blood serum, except so far as the spinal fluid, as it gradually becomes colorless, contributes its pigment to the blood serum in the process of absorption. In some cases in which cerebral hemorrhage has been present, this contribution of pigment may so elevate the icterus index of the serum that clinical jaundice will appear.

Under normal circumstances, that is, when gross cerebral hemorrhage has not occurred, the pigmentation of the cerebrospinal fluid is due to the transudation of plasma pigments during labor. Along with this pigment, as a rule, as indicated by table 3, are varying quantities of red blood cells. The conversion of the hemoglobin of these cells to bilirubin and possibly other pigments causes a gradual rise in the icterus index of the cerebrospinal fluid which reaches its maximum during the second week of life.

COMPARATIVE VAN DEN BERGH REACTIONS OF BLOOD SERUM AND SPINAL FLUID

The van den Bergh reactions of the serum of blood withdrawn from the heart immediately after death were compared in eight cases with the same reactions of clear yellow spinal fluids which gave a negative benzidine reaction and which were obtained by lumbar puncture from the same patients immediately after death. These cases are recorded in table 8. The diagnosis in every instance, except in case 1, was checked by necropsy.

A positive indirect van den Bergh reaction was obtained from the blood serum in every case. When the reaction was delayed (cases 2 and 8), the reactions of the spinal fluid were negative. In the remaining six cases in which the reaction was immediately positive in the blood serum, the indirect van den Bergh reaction of the spinal fluid was negative in two cases, delayed and faint in three cases, and only immediately positive in one case (case 5), a patient with a subarachnoid hemorrhage.

The direct van den Bergh reaction in seven of the same specimens of blood serum was negative in three cases and faint and delayed in

TABLE 8.—*Comparative van den Bergh Reactions of Blood and Cerebrospinal Fluid*

Case	Diagnosis	Age in Days	Van den Bergh Reactions			
			Indirect		Direct	
			Blood	Spinal Fluid	Blood	Spinal Fluid
1	Cerebral hemorrhage ?.....	⅛	Moderate immediate positive	Faint delayed positive	Faint delayed positive	Negative
2	Enlarged thymus; congenital heart disease	⅔	Moderate delayed positive	Negative	Negative	Negative
3	Congenital heart disease....	1⅛	Moderate immediate positive	Negative	Negative	Negative
4	Enlarged thymus; slight subarachnoid hemorrhage	5	Strong immediate positive	Faint delayed positive	Moderate delayed positive	Faint delayed positive
5	Subtentorial hemorrhage; otitis media	8	Strong immediate positive	Moderate immediate positive	Strong immediate positive	Moderate delayed positive
6	Pneumonia	18	Moderate immediate positive	Faint delayed positive	Not done	Negative
7	Otitis media; bronchitis.....	25	Moderate immediate positive	Negative	Moderate immediate positive	Negative
8	Streptococcus septicemia.....	42	Faint delayed positive	Negative	Negative	Negative

one. The corresponding direct van den Bergh reactions on the cerebrospinal fluid were negative. In another instance, case 7, in which the direct reaction of the blood serum was moderately strong and immediately positive, the direct reaction of the spinal fluid was negative.

In cases 4 and 5, in which the direct reactions in both blood and spinal fluid were positive, cerebral hemorrhage had occurred.

The foregoing series of cases is small but suggests that, while in general there is a parallelism between the intensity of the van den Bergh reactions in blood serum and in cerebrospinal fluid, the relationship is probably much the same as that already described between the icterus index of blood serum and the icterus index of cerebrospinal fluid.

While bilirubinemia probably does not contribute to the presence of bile in the cerebrospinal fluid, except possibly in unusual circumstances, such as occur in kern icterus, it is possible that in cases of hemorrhage of the central nervous system, as the bile pigments are absorbed from the spinal fluid, bilirachia may contribute to bilirubinemia. This problem awaits further elucidation through the study of comparative quantitative van den Bergh reactions of blood and cerebrospinal fluid.

COMPARISON OF SPINAL AND VENTRICULAR FLUIDS

In the discussion regarding the methods by which the cerebrospinal fluids of this study were obtained, it was stated that the principal reason for abandoning ventricular punctures was the fact that traumatic hemorrhages were sometimes produced which could not be distinguished, except occasionally with great difficulty, from antemorten hemorrhages. Another reason for abandoning ventricular puncture was the large number of dry taps. It is extremely difficult to obtain fluid from the ventricles of premature infants unless the ventricles are abnormally

TABLE 9.—*Comparison of Spinal and Ventricular Fluids*

	Number of Cases	
	Clear Fluid	Bloody Fluid
Spinal puncture	9	5
Ventricular puncture	7	7

distended. At necropsy the ventricles are invariably found collapsed, making it practically impossible to secure fluid, even by dissection through the brain substance. Schmorl [74] commented on the difficulty of securing ventricular fluid uncontaminated by blood from the brains of adult cadavers.

The cases in which both lumbar and ventricular punctures were performed are recorded in table 9. The paucity of the cases in this series does not warrant a review of the literature regarding the differences in properties which have been reported between ventricular and spinal fluid.[80] The spinal punctures were attempted before the ventricular punctures, because experience had shown that they were more likely to be successful as regards freedom from contamination by traumatic blood than the ventricular punctures. In two cases in which the spinal and ventricular fluids were both bloody, extensive cerebral hemorrhage, both supratentorial and infratentorial, was present. In another case there was only a moderate hemorrhage. In only one of the two cases in which bloody fluid was obtained from the ventricles and clear fluid from

80. Cushing, Harvey: Studies on Cerebrospinal Fluid, J. M. Research **31**:1 (Sept.) 1914. Schmorl, G. (footnote 74).

the spinal canal was evidence found at necropsy to explain a difference in the type of fluid obtained by the two routes. This case has been previously discussed as case 3 of table 4.

In seven instances, clear spinal and ventricular fluids were obtained from the same patient. The color of the fluids in the same patient was always identical. In three cases the fluids were colorless. These patients were over 2 months old. In three infants, aged 1 hour, 28 and 42 days, respectively, the fluids were faintly yellow. In one case, that of a patient aged 5 days, with kern icterus, the fluids were deep yellow. In the patients with yellow fluids the van den Bergh reactions were negative in every instance except that of the infant with kern icterus, in whom the reactions on both fluids were the same.

The fact that the color and the van den Bergh reactions of the specimens of cerebrospinal fluid from the ventricles and spinal canal were always identical in the same patient might be considered as indicating the origin of the pigment by excretion or transudation through the choroid plexus. However, the work of Dandy and Blackfan [81] and others [82] on the diffusibility of neutral phenolsulphonphthalein in cerebrospinal fluid suggests that the uniformity in properties of the two fluids may be due to a high degree of diffusibility of the yellow pigment, possibly from a source of origin outside of the ventricles.

KERN (NUCLEAR) ICTERUS

The term "kern icterus" deserves explanation because, although the condition which it denotes is well known to German pathologists, it is almost unmentioned in English literature, except for a brief description by Abt.[83] The term was first introduced by Schmorl [84] in 1903 to describe a condition of the brain occurring in some cases of severe jaundice in which the cells of certain cranial nuclei, particularly the hypothalamus, hippocampus, nucleus dentatus and the sensory nuclei of the medulla oblongata are stained yellow more or less deeply in sharp contrast to the surrounding nervous tissue. Schmorl called this condition "Kernikterus," a word which is easily anglicized to "kern icterus,"

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81. Dandy, W. E., and Blackfan, K. D.: An Experimental and Clinical Study of Internal Hydrocephalus, J. A. M. A. **61**:2216 (Dec. 20) 1913.

82. Solomon, H. C.; Thompson, L. J., and Pfeiffer, H. M.: Circulation of Phenolsulphonphthalein in the Cerebrospinal System, J. A. M. A. **79**:1014 (Sept. 23) 1922.

83. Abt., I. A.: Familial Icterus of New-Born Infants, Am. J. Dis. Child. **13**:231 (March) 1917.

84. Schmorl, G.: Zur Kenntnis des Icterus neonatorum, insbesondere der dabei vorkommenden Hirnveränderung, Verhandl. d. deutsch. path. Gesellsch. **6**:109, 1903.

although there is no good reason why the literal translation of the term, "nuclear icterus," should not be used. Such staining of the cranial nuclei had been noted previously by Orth,[85] in 1875. Apparently it is not common, and in Schmorl's series of 120 necropsies on patients who had had icterus neonatorum it occurred only six times, or in 5 per cent of the cases.

Kern, or nuclear, icterus, is not to be confused with the faint yellow diffuse coloration of the brain commonly found in all forms of severe jaundice of the new-born. Kern icterus has never been described in an adult. Its presence is probably not altogether dependent on the degree of jaundice. In the most severely jaundiced infant of our series, a premature infant aged 8 days, who weighed 1,375 Gm., kern icterus was suspected during life because of the severity of the jaundice. At necropsy, performed immediately after death, kern icterus was not found. The icterus index of the heart's blood at the time of death was 169, one of the highest ever observed at this hospital. The pigment in kern icterus probably differs from ordinary bile pigment because its color rapidly disappears in the presence of light, and is destroyed by solution of formaldehyde, bichloride of mercury and other reagents. The etiology of the condition is unknown.

In addition to the cases reported by Orth and Schmorl, cases have been described principally by von Beneke,[86] Esch,[87] Pfältzer,[88] Hart,[89] Palm,[90] von Gierke [91] and Ylppö.[92] A complete discussion of the subject of kern icterus with a review of the literature, the pathologic observations, the theories of its etiology and the complete details of the cases reported, is beyond the scope of the present study.

Two cases of kern icterus occurred in this series; unfortunately this was early in the work when the icterus index was not being studied and van den Bergh tests on the blood serum were not being made.

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85. Orth, J.: Ueber das Vorkommen von Bilirubinkrystallen bei neugeborenen Kindern, Virchows Arch. f. path. Anat. **63**:447, 1875.

86. Von Beneke, R.: Ueber Kernicterus der Neugeborenen, München. med. Wchnschr. **32**:30, 1908; Ueber Kernikterus der Neugeborenen, ibid. **59**:387, 1912.

87. Esch., P.: Ueber Kernikterus der Neugeborenen, Zentralbl. f. Gynäk. **32**:30, 1908.

88. Pfältzer, B.: Der Kernicterus der Neugeborenen eine Infectionskrankheit, Ztschr. f. Geburtsh. u. Gynäk. **76**:685, 1915..

89. Hart, C.: Ueber den Kernikterus der Neugeborenen, Berl. klin. Wchnschr. **54**:70, 1917.

90. Palm, H.: Zur Frage der Entstehung des Kernikterus der Neugeborenen, Monatschr. f. Geburtsh. u. Gynäk. **49**:264, 1919.

91. Von Gierke, E.: Kernikterus und Erythroblastose, Verhandl. d. deutsch. path. Gesellsch. **18**:322, 1921.

92. Ylppö, A.: Zur Klinik und Aetiologie des familiären Icterus neonatorum gravis, Ztschr. f. Kinderh. **17**:334, 1918.

The first case has been described previously, in part, as case 4 of table 4. This was in a white male infant who weighed 1,565 Gm. at birth and was of about twenty-six weeks' gestation, according to the history. The child's skin was red during life, and jaundice, which was moderate, was noticed only after the skin became pale when the infant died at the age of 5 days. Lumbar puncture was performed immediately after death, and a clear, deep yellow fluid not containing red blood cells and giving a negative benzidine reaction was obtained. The indirect van den Bergh reaction of the spinal fluid was faintly positive. The direct van den Bergh reaction was delayed and faint. At necropsy the usual manifestations of kern icterus were present, and in addition there was a subarachnoid, subtentorial hemorrhage.

The second case of kern icterus occurred in a colored male infant of about thirty weeks' gestation, who weighed 1,330 Gm. at birth. The child's progress was uneventful until about the age of 8 days, when diarrhea developed. Jaundice involving the sclerotics was noticed on the tenth day. Possibly an earlier cutaneous icterus was not noticed because of the naturally dark color of the infant's skin. Death occurred at the age of 12 days, and a lumbar puncture was done immediately afterward. The spinal fluid was clear and moderately yellow and contained a microscopic number of red blood cells. The benzidine test on the

TABLE 10.—*Data of Material from which Details of Study Were Drawn*

	Number	Per Cent
Premature infants in the series	100	
Deaths	81	81
Necropsies	70	80
Total lumbar punctures	129	
Punctures on living infants	63	49

fluid was negative. The indirect van den Bergh reaction of the spinal fluid was faint and immediately positive; the direct reaction was delayed and moderately positive. Postmortem examination revealed only the usual cranial changes observed in kern icterus.

SUMMARY

One hundred infants were studied and 129 lumbar punctures performed, 49 per cent of which were made during life and the remainder immediately after death. The material from which the details of this study were drawn is briefly recapitulated in table 10.

The smallest infant of the series in whom puncture was performed during life was ½-hour old and weighed 885 Gm.

The explanation for the frequency of faulty lumbar punctures in premature infants is shown to be the detachment of the posterior wall of the dura mater spinalis by the entering needle and the pushing over this posterior wall against the anterior wall, resulting in a dry tap. If the needle pierces both layers of the dura and enters the venous plexus on the posterior wall of the canal or the highly vascular body of a vertebra, a tap contaminated by traumatic blood may result.

It is suggested that this may be the explanation of occasional unsuccessful punctures in older children and in adults.

Based on anatomic and physical considerations, a technic was developed by which the percentage of faulty lumbar punctures in premature infants was reduced from 35 to 20 per cent.

The principle of the technic consists in the employment of a small hypodermic needle (no. 27) for performing the puncture and having the infant held in a sitting position so that the lumbar portion of the dural sac is distended by the pressure from above of the column of fluid within it.

Ill results have not been seen from the employment of this technic on living premature infants, and the procedure has often been of great value in the diagnosis and treatment of cerebral hemorrhage.

There is no doubt, however, that accidents can occur in premature infants, as in adults, following lumbar puncture when, by reason of the presence of hydrocephalus or a blood clot in the proper location, the foramen magnum may be plugged and fatal pressure exerted on the medulla oblongata.

In a series of twenty-six cases of cerebral hemorrhage proved by necropsy, the cerebrospinal fluid obtained by lumbar puncture was grossly bloody or hazy in nineteen cases, or 73 per cent.

In a series of forty-two cases in which evidence of cerebral hemorrhage was not found at necropsy, the spinal fluid was grossly bloody or hazy in thirteen, or 31 per cent, of the cases. This percentage, if the technic previously mentioned had been employed through the series, would have been reduced to 20 or less, but even this percentage is sufficiently high to indicate the danger of making a diagnosis of cerebral hemorrhage only on the basis of bloody spinal fluid withdrawn by lumbar puncture.

Spinal fluids free from microscopic red blood cells occur but rarely during the first two weeks of life. The probability of finding such fluid increases rapidly with the age of the infant.

The presence of red blood cells in microscopic numbers in the cerebrospinal fluid of premature infants during the early days of life is so common that it may be considered as a physiologic phenomenon.

The difficulty of distinguishing at lumbar puncture between fluids bloody as the result of trauma and fluids which contain blood as the result of intracranial hemorrhage is discussed. The opinion is expressed that it is not always possible to make such a differentiation.

As an aid in making the differentiation already mentioned, it is shown that when the proper precautions are taken to avoid hemolysis, the benzidine test on the supernatant fluid after it is centrifugalized will be positive in about 50 per cent of the cases when cerebral hemorrhage is present and negative in every case when the blood is of traumatic origin.

Crenated red blood cells in cerebrospinal fluid are regarded as cells which were in the fluid previous to the time of the lumbar puncture at which they were obtained.

Seven cases of subtentorial intracranial hemorrhage in premature infants varying in age from 8 hours to 22 days in which the spinal fluid obtained by lumbar puncture was free from gross, and occasionally also from microscopic, blood are recorded.

It is shown that clear spinal fluid may be obtained in certain cases of cerebral hemorrhage, even during the first day of life when the hemorrhage is fresh, because the location of such hemorrhages is beneath the pia mater, thus preventing any significant admixture of blood and cerebrospinal fluid. Probably also in some subarachnoid hemorrhages, the bleeding is localized by the formation of clots, which is favored by the presence of numerous subarachnoid trabeculae in certain locations.

A brief history of yellow pigmentation of the cerebrospinal fluid is given and a method of measuring the degree of pigmentation, or xanthochromia, quantitatively by means of the icterus index is described.

Every cerebrospinal fluid in this series obtained from a premature infant under the age of 60 days showed some degree of pigmentation varying from a pale, scarcely perceptible straw color to a deep brownish yellow.

Yellow pigmentation of the cerebrospinal fluid of premature infants occurs so constantly during the early weeks of life that it may be considered as a physiologic phenomenon.

The icterus index of the water-clear cerebrospinal fluids of this series which gave negative benzidine tests varied between 0 and 11.

The average icterus index of the cerebrospinal fluid, when all the cases of the series are included, is about 1 during the first twenty-four hours of life; this increases rather rapidly, attaining a maximum of about 3½ during the second week and then gradually decreasing to 0 at about the age of 60 days, or probably in some cases at a somewhat earlier age.

If the cases showing postmortem or clinical signs of cerebral hemorrhage were ruled out of the foregoing series, the general form of the curve representing the icterus index of the cerebrospinal fluid would be the same, but the height of the curve would be lower and probably would not rise over 2½ as a maximum.

The van den Bergh test for bilirubin in cerebrospinal fluid (bilirachia) is described.

The van den Bergh reaction, like the icterus index, is considered only in the cases of water-clear fluids which gave a negative benzidine reaction.

The indirect van den Bergh reaction was positive in twenty-one cases, or 60 per cent, of the yellow spinal fluids of this series.

An immediately positive direct van den Bergh reaction occurred only once in this series, and in that case the reaction was distinctly biphasic. This fluid had an icterus index of 5 and was obtained from

a patient with marked icterus who died at the age of 23 days of hydrocephalus, which presumably was secondary to an intracranial hemorrhage.

Levinson's [18] observations regarding the presence of yellow cerebrospinal fluids which give neither a positive benzidine nor a positive van den Bergh reaction are confirmed, and I agree with his suggestion that this is due to a yellow pigment which is perhaps an intermediate compound between hemoglobin and bilirubin.

It is shown that the relative height of the icterus index of both the cerebrospinal fluid and the blood serum of premature infants is largely independent of the presence (in the case of the spinal fluids) or the degree of intensity of the van den Bergh reaction. This is probably due, at least in part, to the presence of the pigment previously mentioned.

Evidence is given to show the autochthonous production of this pigment and bilirubin following hemorrhage into the cerebrospinal fluid, and that this has an important influence on the degree of xanthochromia of the cerebrospinal fluid.

The literature regarding the relationship between icterus and yellow cerebrospinal fluid is reviewed, and from this it is concluded that while xanthochromia occurs, independent of hemorrhage, rather infrequently in icterus, its presence presumably means the appearance of another factor such as damage to the choroid plexus or the ependyma. Furthermore, the yellow pigment of the cerebrospinal fluid in icterus may not always give a positive reaction for bile pigment.

Yellow pigmentation of the cerebrospinal fluid of premature infants during the first few weeks of life is probably due to a combination of factors. These factors, which may also be concerned with xanthochromia in new-born, full term infants, are:

1. During the First Few Days of Life.

   (*a*) The possibility of the antenatal secretion of yellow pigment through the choroid plexus.

   (*b*) Transudation of blood plasma with its pigments through the congested cerebrospinal vessels during labor.

2. After the First Few Days of Life.

   (*a*) Hemolysis of the red blood cells which have entered the cerebrospinal fluid during labor as a result of diapedesis or capillary or grosser forms of hemorrhage, with the rapid conversion of the hemoglobin to a yellow pigment, which gives neither a benzidine reaction nor a positive van den Bergh reaction, and also to bilirubin.

   (*b*) In certain cases of icterus gravis (due to sepsis or other causes) or of kern (nuclear) icterus, it is possible that the bilirubinemia contributes to the xanthochromia. The pathway by which the pigment enters the cerebrospinal fluid is perhaps by secretion through the choroid plexus, damaged by the intensity or nature of the bilirubinemia, or by transudation or osmosis through the other cerebrospinal vessels.

Evidence is presented which strongly suggests that cerebral hemorrhage may influence the degree, and is occasionally responsible for, the presence of some cases of icterus neonatorum.

A comparison is made between cerebrospinal fluid obtained at the same time from the cerebral ventricles and the spinal canal. In seven cases in which clear fluid was obtained from both sources, the color and van den Bergh reactions of the two fluids were identical.

Kern, or nuclear, icterus is briefly described, and the observations on the spinal fluid in two cases are reported.

CONCLUSIONS

The most frequent cause of unsuccessful lumbar punctures in premature infants is the pushing forward of the loosely attached dura of the posterior wall of the spinal canal by the entering needle.

Unsuccessful lumbar punctures will occur much less frequently if the tap is made with the child sitting in an upright position and when a fine hypodermic needle is used.

Lumbar puncture in premature infants, if the proper technic is used, is a relatively safe procedure and is often of great value in the diagnosis and treatment of cerebral hemorrhage.

Bloody spinal fluid obtained from these infants is suggestive but not diagnostic of intracranial hemorrhage.

Blood due to the trauma of the puncture frequently cannot be differentiated from blood present as the result of intracranial hemorrhage.

The presence of red blood cells in microscopic numbers in the spinal fluid of premature infants during the early days of life is a physiologic phenomenon.

The most common form of intracranial hemorrhage in premature infants is the subpial hemorrhage.

Fatal cerebral hemorrhages may occur in premature infants without the appearance of gross blood or even an exceptional number of microscopic red blood cells in the spinal fluid.

Xanthochromia is a physiologic phenomenon in premature infants during at least the first four weeks of life.

The degree of xanthochromia of cerebrospinal fluid may be conviently measured quantitatively by means of the icterus index.

The icterus index of the cerebrospinal fluid of premature infants is highest during the second week of life.

More than half of the yellow spinal fluids of these infants give a positive indirect van den Bergh reaction.

Yellow spinal fluids occur with a relatively high icterus index, which give neither a positive benzidine test nor a positive van den Bergh reaction. The color of these fluids is presumably due neither to

hemoglobin nor to bilirubin but probably to a pigment or pigments intermediate in composition between these two.

A positive direct van den Bergh reaction of spinal fluid is strongly suggestive that the patient has had an intracranial hemorrhage. It may, however, occur in kern icterus without cerebral hemorrhage.

Cerebral hemorrhage probably contributes to the degree of icterus neonatorum, and unrecognized cerebral hemorrhage is perhaps the cause of some cases of so-called "physiologic" icterus neonatorum.

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THE VOLUME OF THE BLOOD

II. THE VOLUME OF THE BLOOD AND CONCENTRATION OF CRYSTALLOIDS AND ELECTROLYTES IN DEHYDRATION AND EDEMA *

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For a number of years, much interest has attached to the general problem of dehydration and especially to the changes that occur in the blood with undue loss of water from the body. As a review by Marriott [1] has appeared recently, an attempt is not made here to recapitulate the early literature except so far as the work of previous investigation bears directly on the present subject.

In approaching this problem in infants and children, one is more or less limited to the use of physical methods, since accurate chemical analyses of the several components usually require quantities of blood too great to be withdrawn with safety from the dehydrated infant. Also, as data obtained by physicochemical methods have already been reported by Salge,[2] Lust,[3] Reiss,[4] and Berend and Tezner,[5] it seemed of first importance to correlate the facts revealed by the physicochemical examination of the blood with the results of determinations of blood volume. As the same methods should give equally interesting data concerning states characterized by retention of water, such cases were also studied. Answers were sought in particular to the two questions that arise; first, is there a diminution of the plasma volume in dehydra-

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1. Marriott, W. McKim: Anhydremia, Physiol. Rev. **3**:275, 1923; Some Phases of the Pathology of Nutrition in Infancy, Am. J. Dis. Child. **20**:461 (Dec.) 1920.

2. Salge, B.: Die physikalischen Erscheinungen des Blutes beim gesunden und kranken Saüglingen, Ztschr. f. Kinderh. **1**: 426, 1911.

3. Lust, F.: Ueber den Wassergehalt des Blutes, Jahrb. f. Kinderh. **73**:85 and 179, 1911.

4. Reiss, E.: Die refraktometrische Bluterscheinungen, Ergebn. d. inn. Med. u. Kinderh. **10**:53, 1913; Untersuchungen der Blutkonzentration des Saüglings, Jahrb. f. Kinderh. **70**:311.

5. Berend, N., and Tezner, E.: Die Wasserentziehung im Saüglingsorganisums bei akuten Gewichtsschwankungen, Monatschr. f. Kinderh. **10**:213, 1911.

tion and edema? and second, if so, is the diminution a simple dehydration or is the concentration of the plasma maintained at a constant level with respect to crystalloids, regardless of the plasma volume?

Marriott [6] and Utheim [7] pointed out the importance of diminution of blood volume in causing the symptoms of dehydration. They emphasized, also, the slowing of blood flow and presented figures showing the rate in the arm to be about one-tenth of the normal. Utheim found similar conditions in rabbits rendered anhydremic by starvation. Gesell [8] and his co-workers studied the effects of reduced blood volume induced by hemorrhages in dogs. They found a decreased rate of blood flow, decreased oxygen consumption, and increased respiratory response to breathing air containing increased quantities of carbon dioxide. Most of the symptoms could be relieved by giving saline solution alone. Keith [9] found a normal arterial oxygen saturation with diminished venous oxygen saturation in dogs with artificially produced dehydration. This is further indirect evidence of slowing of the blood flow. Schloss [10] found that intravenous injections of hypertonic salt solutions in conjunction with subcutaneous injections of saline solution gave temporary relief from some of the symptoms of anhydremia, but that a ten per cent solution of dextrose, given intravenously, gave more lasting effects. He attributed the difference to the fact that the sodium chloride solution made the blood hypertonic and thus led to further anhydremia through diuresis. On the other hand, the dextrose solution attracted water from the saline solution given subcutaneously, but owing to the combustion of the dextrose the plasma did not long remain hypertonic. The point to be emphasized is that even a temporary increase in the blood volume gave relief from the symptoms of dehydration. This is, of course, universally admitted now.

If the pathologic physiology of anhydremia in infants is analogous to that of cholera, one would expect a marked increase in the viscosity of the blood, due probably to an increased concentration of the red blood corpuscles. Marriott [6] assumed that the change in viscosity might

6. Marriott (footnote 1, second reference).

7. Utheim, K.: Advanced Chronic Nutritional Disturbances in Infancy, J. Metabol. Res. **1**:803, 1922.

8. Gesell, R.; Blair, E., and Trotter, R. T.: On the Relation of Blood Volume to Tissue Nutrition, Am. J. Physiol. **61**:399, 1922. Gesell, R.; Capp, C., and Foote, F.: On the Relation of Blood Volume to Tissue Nutrition, ibid. **63**:1, 1922.

9. Keith, N. M.: Blood Volume Changes Following Water Abstinence, Am. J. Physiol. **59**:452, 1922; Circulatory Changes in Experimental Dehydration, ibid. **63**:394, 1923.

10. Schloss, O. M.: Treatment of Dehydration in Infants, Boston M. & S. J. **187**:427, 1922.

account for some of the symptoms seen in infants with dehydration. Moreover, Lust [11] found a moderate increase of viscosity in cases of intoxication. However, in none of his cases of intoxication did the viscosity values approach the figures for the blood viscosity of the newly born, in whom there is generally a marked polycythemia. To what extent, then, changes in viscosity, blood volume and rate of blood flow are the causes of symptoms in anhydremia remains to be determined.

The present study is concerned principally with the changes in the blood volume and the concentration of the plasma in infants with dehydration. For the sake of comparison, we have included also a number of infants showing a tendency to retention of water. In the cases here presented, the following determinations were made: the volume of the blood and the proportion of plasma to corpuscles, the protein concentration of the serum, the freezing point of the serum, the electrical conductivity of the serum, and the sodium chloride content of the serum (or plasma). For various reasons, all of these determinations could not be done in every instance, but the data are sufficiently complete to warrant discussion.

METHODS

Blood Volume.—Blood volume was determined by the method of Keith, Rowntree and Geraghty,[12] slightly modified for use with infants and children.

After removing blood for the control, a measured quantity, from 8 to 10 cc., of vital red solution was injected intravenously. Dye solutions of different concentrations were used, so that 1.5 mg. of dye per kilogram of body weight could be injected in from 7 to 10 cc. of salt solution. The control specimen of blood was mixed with sodium oxalate and used for determination of the cell volume, and the specimen obtained after the dye solution was injected was allowed to clot. The serum obtained in this way was used for the determination of conductivity and freezing point. This did not introduce any detectable error in the determinations of freezing point or conductivity and did away with the error in the determination of plasma volume that would have been brought about by adding hypertonic oxalate.

The volume percentage of red corpuscles was then determined by centrifugalizing the oxalated blood under mineral oil for 20 minutes at 20,000 revolutions per minute in hematocrit tubes made from Folin-McElroy sugar burets calibrated with mercury. Hooper and others [13] pointed out that diffusion of water from the red cells into the plasma, when hypertonic oxalate is added to blood, may produce an error as large as 3 per cent in the hematocrit reading. Loss of carbon dioxide

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11. Lust, F.: Die Viscosität des Blutes beim gesunden und kranken Saüglingen, Arch. f. Kinderh. **4**:260, 1910.

12. Keith, N. M.; Rowntree, L. G., and Geraghty, J. T.: A Method for the Determination of Plasma and Blood Volume, Arch. Int. Med. **16**:219 (Oct.) 1915.

13. Hooper, C. W.; Smith, H. P.; Belt, S., and Whipple, G. H.: Experimental Control of a Dye Blood Volume Method, Am. J. Physiol. **51**:205, 1920.

also can produce a shrinkage in the cell volume as great as 2 per cent, but the error from this source is probably negligible in the case of blood specimens kept from exposure to air by the use of paraffin oil. Therefore, in the cases here reported the per cent by volume of the red cells is probably about 3 per cent too low, but the error is almost constant throughout the series and the results are sufficiently accurate for our purposes. It must be borne in mind, however, that, as Utheim [7] pointed out, in infants with dehydration the red cells tend to pile up in the capillaries so that the venous blood contains a smaller proportion of red corpuscles than the rest of the blood. This is true of other conditions in which failing circulation is present, such as surgical shock and shock resulting from the administration of histamine. Moreover, leaving a tourniquet on the arm produces considerable concentration of the blood (Peters and others [14]). In the infants that we studied the jugular vein was used so that such an error did not occur in these cases. In children a tourniquet was used, but the length of time it was kept in place was so short that great error in the plasma volume or percentage volume of red cells could not have been introduced from this cause.

All the methods for determining the blood volume have been criticized by Erlanger [15] and by Sampson and Rosenthal.[16] It cannot be said that the total volume of the blood can be accurately measured in any method, and the results obtained by the different methods differ considerably. However, we are convinced that the dye method does give results which are sufficiently accurate for comparative purposes. Repeated determinations done on the same patient, reasonably near together, give practically identical results.

TABLE 1.—*Data of Blood Volume*

	Blood Volume before Transfusion				Blood Given in Transfusion				Blood Volume after Transfusion			
Case	Serum Protein, Gm.	Whole Blood, Cc.	Plasma, Cc.	Cells, Cc.	Serum Protein, Gm.	Whole Blood, Cc.	Plasma, Cc.	Cells, Cc.	Serum Protein, Gm.	Whole Blood, Cc.	Plasma, Cc.	Cells, Cc.
1	31.5	542	350	192	10.6	230	123	107	40.2	639	435	204
2	31.6	759	408	351	10.1	229	120	100	40.7	864	535	329

That the vital dye method gives reasonably reliable results for plasma, moreover, is illustrated by certain observations which we have made in conjunction with Dr. George Kahn. In a series of patients not showing evidence of disturbance of water balance, determinations of the volume of the cells and the volume and the protein content of the plasma were done immediately previous to the introduction into the peritoneal cavity of a definite quantity of blood, of which the percentage by volume of cells and the protein concentration of the plasma were known. Twenty-four hours later, the determinations of blood volume and protein concentration were repeated. Regarding the cells little can be inferred, owing presumably to their slow absorption. However, the agreement between the expected values for the volume of the plasma and the quantity of protein contained in it, and the values actually found, is so striking that the results observed in two typical cases are here reported in table 1.

14. Peters, J. P.; Bulger, H. A.; Eisenman, A. J., and Lee, C.: Total Acid-Base Equilibrium of Plasma in Health and Disease, J. Biol. Chem. **67**:175, 1926.

15. Erlanger, J.: Blood Volume and Its Regulation, Physiol. Rev. **1**:177, 1921.

16. Sampson, P. D., and Rosenthal, S. M.: The Inadequacy of Our Present Blood Volume Methods, Am. J. Physiol. **63**:357, 1923.

Protein Concentration.—The concentration of serum protein was determined by the use of an Abbé refractometer. The readings of the refractometer were converted into percentage of serum protein by the following formula:

$$\frac{R\text{-}R_1 - 0.0022 \times 100}{0.00172} = \% \text{ of serum protein}$$

Here R = Refractive index of the serum at 20 C.
R_1 = the refractive index of water.
0.0022 = correction for nonprotein constituents of the blood.

Conductivity.—The electrical conductivity of the serum at 20 C. was determined by the usual Kohlrausch method, a specially designed cell that we have described being used. We have followed the suggestion of Gram and Cullen [17] and have expressed our results in terms of solutions of pure sodium chloride in conductivity water. We have also used Gram's correction for the influence of the serum protein on conductivity.

The determination of the conductivity of the true serum, or plasma, would necessitate the separation of the fluid from the corpuscles, under oil, in order to prevent the escape of carbon dioxide and the corresponding increase in the chloride ion content of the plasma. In the results here recorded it is recognized that this error is present, but we believe that its magnitude is such that it does not influence the conclusions that have been drawn from the values which we obtained.

Freezing Point.—The freezing point of the serum was determined by means of a thermocouple that we [18] have designed.

Tezner and Poka [19] pointed out that, due to adsorption of crystalloids by colloids, the freezing point of blood is not a true measure of the concentration of substances in the blood. Since the maximum error they produced, by adding colloids to solutions of pure crystalloids, is +0.0015 C., failure to take this into account in our determinations would not appreciably alter the sense of our results. A more important source of error is that due to lowering the bicarbonate content of the serum, or plasma, which occurs when the whole blood is exposed to atmospheric air. This, we have shown, may amount to as much as 0.04 C. This error would parallel the error involved in calculating the bicarbonate content of the serum, by subtracting from its total conductivity the calculated fraction due to sodium chloride, and expressing the difference in terms of sodium bicarbonate. Hence, in tables 2, 3 and 4, although the values for observed freezing points and

17. Gram, H. C., and Cullen, G. E.: The Accuracy of the Ionometric Method and the Protein Corrections in Measuring Serum Conductivity, J. Biol. Chem. **57**:477, 1923.

18. Darrow, D. C., and Buckman, T. E.: The Use of the Thermocouple in Determining the Freezing Point of a Small Quantity of Fluid, Am. J. Dis. Child., to be published.

19. Tezner, B. and Poka, J.: Beitrage zur Analyse der Gefrierpunkterniedrigung physiologischer Flüssigkeiten, Ztschr. f. physiol. Chem. **56**:495, 1908.

the calculated bicarbonate contents do not represent accurately the values which would be obtained in the case of true serum, or plasma, it is nevertheless probable that the fractions of the total freezing point depression, represented by the estimated bicarbonate contents, are approximately true.

The importance of variations in bicarbonate content of the plasma, due to changes in the concentration of carbon dioxide in the environment to which the blood is exposed, is the subject of another paper by us.[20]

It has been the custom to speak of the freezing point depression, rather than the freezing point of a solution. The custom, of course, grew out of the practice of determining the influence on the freezing point of a solution of the addition to it of known quantities of solute. However, in these experiments such a procedure was not used, and we have therefore adopted the simpler expression, freezing point, except when speaking of the fractional parts of the total freezing point depression caused by different substances.

Chlorides.—Chlorides were determined by the method of Millard Smith.[21] Venous serum or plasma kept under mineral oil was used.

RESULTS

The results of our investigations are shown in tables 2, 3 and 4.

The patients are divided into two main groups: those not showing evidence of disturbance of water balance and those showing some disturbance of water metabolism on one or more occasions. The former group is again divided into those not showing any abnormality other than undernutrition, and those with miscellaneous diseases. The patients with disturbance of water balance are also subdivided into: those with a tendency to dehydration of the tissues; and those with a tendency to retention of water in the tissues.

For the most part, the arrangement of the results in the tables is self-evident. In calculating the fraction of the freezing point depression caused by sodium chloride and sodium bicarbonate, the dissociation constants of these substances were taken to be 0.9 and 0.6, respectively. It was also assumed that the conductivity fraction not accounted for by sodium chloride was due entirely to sodium bicarbonate, the other electrolytes being quantitatively insignificant for the purpose presently under consideration. There is some error involved in calculating the quantity of sodium bicarbonate from the determinations of conductivity, as we have been unable to find values for the conductivity of sodium bicarbonate in colloidal solutions, and our estimates are reckoned on the basis of pure solutions of sodium bicarbonate. The absolute error, however, is probably small and consistent throughout the series. In estimating the fraction of the freezing point depression caused by the serum protein, it was assumed that a 1 per cent solution would give a freezing point of 0.00138 C. This is the value given by Sabanejeff and Alexandrow.[22] Bugarszky and Liebermann,[23] however, obtained

20. In preparation.

21. Smith, Millard: Determination of Chlorides, J. Biol. Chem. **45**:437, 1921.

22. Sabanejeff, A., and Alexandrow, U.: Ueber das Moleculargewicht des Eieralbumins, Ztschr. f. physiol. Chem. **9**:88, 1892.

23. Bugarsky, S., and Liebermann, L.: Ueber das Bindungsvermögen eiweissartigen Körper für Salzsaüre, Natrium, und Kochsalz, Arch. f. d. ges. Physiol. **72**:151, 1898.

TABLE 2.—*Data of Patients with Normal Water Metabolism*

Clinical Notes					Volume of Blood						Concentration of Red Blood Cells and Serum Protein				Concentration of Electrolytes of Serum						Concentration of Crystalloids in Terms of Freezing Point									
Case	Age in Years	Weight in Kg.	Date	Clinical Manifestations	Blood, Cc.	Plasma, Cc.	Cells, Cc.	Blood, Cc. per Kg.	Plasma, Cc. per Kg.	Cells, Cc. per Kg.	Red Blood Cells, % by Volume	Serum Protein, Gm.	Serum Protein, Gm. per Kg.	Serum Protein, %	Conductivity of Serum	Corrected Conductivity	Chlorides, Millimols	Bicarbonates, Millimols	Osmolar Concentration of electrolytes	% of Electrolytes as Chlorides	Freezing Point, Degrees	Part by Sodium Chloride	Part by Sodium Bicarbonate	Part by Electrolytes	Part by Proteins	Part Not Accounted for	% by Sodium Chloride	% by Sodium Bicarbonate	% by Electrolytes	% by Protein	% Not Accounted for
1	2/12	3.33	4/ 6	Undernutrition	...	180	...	...	54	..	..	12	3.6	6.62	685	801	...	...	.....	..	.....	.....	.....	.....	.....	.....	..	..	..	...	..
2	3/12	2.72	7/11	Undernutrition	...	158	...	...	57	..	..	10	3.8	6.57	622	729	...	...	.....	..	0.550	.....	.....	.....	.....	.....	..	..	..	...	..
3	3/12	3.68	10/29	Undernutrition	321	225	96	88	61	26	30	16	4.3	6.97	605	714	...	...	.....	..	0.631	.....	.....	.....	.....	.....	..	..	..	...	..
4	2	7.21	12/ 6	Undernutrition	759	408	351	105	57	49	46	32	4.4	7.78	563	671	103	9	0.213	90	0.568	0.372	0.025	0.397	0.011	0.160	65	4	69	1.7	28
5	2	8.57	12/10	Undernutrition	672	470	202	78	55	24	30	45	5.3	9.60	582	737	102	18	0.226	82	0.570	0.366	0.055	0.421	0.013	0.136	64	10	74	2.3	25
6	2/12	3.66	4/14	Undernutrition	...	...	...	...	..	..	30	..	...	6.90	635	748	...	...	.....	..	0.606	.....	.....	.....	.....	.....	..	..	..	...	..
7	3/12	3.23	7/ 8	Undernutrition	...	...	...	...	..	..	..	..	...	5.95	705	807	...	...	.....	..	0.550	.....	.....	.....	.....	.....	..	..	..	...	..
8	2/12	3.66	8/13	Undernutrition	...	...	...	...	..	..	26	..	...	7.43	647	760	101	22	0.231	78	0.547	0.365	0.061	0.429	0.010	0.109	66	12	78	1.9	20
9	1	....	5/23	Rickets	...	...	...	...	..	..	..	..	...	7.96	680	792	...	...	.....	..	0.526	.....	.....	.....	.....	.....	..	..	..	...	..
10	1	5.42	5/ 5	Rickets, undernutrition	...	...	...	...	..	..	..	..	...	8.02	685	830	...	...	.....	..	0.506	.....	.....	.....	.....	.....	..	..	..	...	..
11	4/12	....	5/15	Tetany	...	...	...	...	..	..	..	..	...	6.45	645	781	...	...	.....	..	0.543	.....	.....	.....	.....	.....	..	..	..	...	..
12	1	10.05	5/10	Tetany	717	515	203	71	50	20	28	30	3.8	7.48	675	808	101	28	0.241	73	0.534	0.364	0.084	0.448	0.010	0.068	68	15	83	1.9	13
13[1]	6/12	4.77	10/15	Tetany	379	242	137	79	51	27	31	18	3.8	7.48	637	753	105	18	0.232	82	0.561	0.378	0.054	0.432	0.010	0.119	67	10	77	1.8	21
13[2]	6/12	5.17	10/29	Tetany; treated with hydrochloric acid	459	318	141	88	62	26	38	24	4.7	8.55	553	664	109	3	0.216	93	0.514	0.391	0.011	0.402	0.012	0.102	76	2	78	2.3	20
14	1	....	5/11	Scurvy	...	...	...	...	..	..	32	..	...	6.51	635	722	96	21	0.218	78	0.513	0.344	0.063	0.407	0.009	0.107	67	12	79	1.7	21
15[1]	3	13.86	9/ 2	Congenital hemolytic jaundice	1147	918	229	83	66	17	20	52	5.9	8.90	650	791	107	21	0.247	79	0.556	0.415	0.045	0.460	0.012	0.084	75	8	83	2.4	15
15[2]	3	13.87	9/ 2	Congenital hemolytic jaundice; transfusion, 170 cc.	1319	970	349	96	70	25	27	89	6.5	9.19	627	768	104	21	0.235	79	0.574	0.373	0.063	0.436	0.013	0.128	65	11	76	2.2	22

TABLE 3.—*Data of Patients with Tendency to Dehydration*

Clinical Notes					Volume of Blood						Concentration of																			
Case	Age in Years	Weight in Kg.	Date	Clinical Manifestations	Blood, Cc.	Plasma, Cc.	Cells, Cc.	Blood, Cc. per Kg.	Plasma, Cc. per Kg.	Cells, Cc. per Kg.	Red Blood Cells, % by Volume	Serum Protein, Gm.	Serum Protein, Gm. per Kg.	Serum Protein, %	Conductivity of Serum	Corrected Conductivity	Chlorides, Millimols	Bicarbonates, Millimols	Osmolar Concentration of electrolytes	% of Electrolytes as Chlorides	Freezing Point, Degrees	Part by Sodium Chloride	Part by Sodium Bicarbonate	Part by Electrolytes	Part by Proteins	Part Not Accounted for	% by Sodium Chloride	% by Sodium Bicarbonate	% by Electrolytes	% by Protein	% Not Accounted for

TABLE 3.—*Data of Patients with Tendency to Dehydration*

Clinical Notes					Volume of Blood						Concentration of Red Blood Cells and Serum Protein				Concentration of Electrolytes of Serum						Concentration of Crystalloids in Terms of Freezing Point									
Case	Age in Years	Weight in Kg.	Date	Clinical Manifestations	Blood, Cc.	Plasma, Cc.	Cells, Cc.	Blood, Cc. per Kg	Plasma, Cc. per Kg	Cells, Cc. per Kg.	Red Blood Cells, % by Volume	Serum Protein, Gm.	Serum Protein, Gm. per Kg.	Serum Protein, %	Conductivity of Serum	Corrected Conductivity	Chlorides, Millimols	Bicarbonates, Millimols	Osmolar Concentration of electrolytes	% of Electrolytes as Chlorides	Freezing Point, Degrees	Part by Sodium Chloride	Part by Sodium Bicarbonate	Part by Electrolytes	Part by Proteins	Part Not Accounted for	% by Sodium Chloride	% by Sodium Bicarbonate	% by Electrolytes	% by Proteins	% Not Accounted for
16[1]	1	4.96	9/16	Undernutrition; chronic dehydration; very sick....	323	200	123	65	40	25	38	17	3.5	8.61	520	632	96	9	0.200	88.5	0.513	0.344	0.028	0.372	0.012	0.129	67	6	73	2.2	24
16[2]	1	5.48	9/20	Same; recovered	476	340	136	87	62	25	29	25	4.5	7.26	...	...	100	..	.....	....	.....	.....	.....	.....	0.010	.....	..	..	..	...	..
17[1]	3	11.36	8/ 8	Encephalitis; very ill, and dehydrated for 4 days..	585	446	139	51	39	12	24	35	3.1	7.96	692	838	119	19	0.259	82.9	0.605	0.426	0.056	0.482	0.011	0.112	70	9	79	1.8	19
17[2]	3	11.45	9/18	Same; better	857	570	287	75	50	25	34	48	4.3	8.49	601	723	103	15	0.225	83.6	0.536	0.372	0.046	0.418	0.012	0.106	69	9	78	2.2	20
18[1]	6/12	6.41	8/ 6	Diarrhea, vomiting, and dehydration; sick 2 days	...	276	...	...	43	..	..	24	3.7	8.61	621	759	...	..	.....	....	0.578	.....	.....	.....	0.012	.....	..	..	..	...	..
18[2]	6/12	6.95	8/15	Same; better	709	434	275	102	62	40	39	28	4.1	6.51	657	754	101	21	0.231	78.8	0.550	0.367	0.063	0.430	0.009	0.111	67	12	79	1.6	20
19[1]	5	10.90	7/19	Lead encephalitis; dehydrated 5 days.....	737	477	260	67	40	22	35	40	3.6	8.12	635	772	100	25	0.231	75.6	0.530	0.358	0.073	0.432	0.011	0.088	68	14	82	2.1	17
19[2]	5	13.16	8/16	Same; better; receiving 600 cc. fifth normal hydrochloric acid daily.....	909	605	304	69	46	23	33	52	4.0	8.67	650	814	129	8	0.261	93.0	0.549	0.463	0.022	0.485	0.012	0.064	76	4	80	2.2	18
19[3]	5	13.31	8/22	Same; better	968	677	291	73	51	22	30	56	4.2	8.24	606	708	110	19	0.245	81.0	0.505	0.396	0.059	0.455	0.011	0.129	67	10	77	1.9	22
19[4]	5	13.75	8/28	Same; receiving 8 Gm. sodium citrate daily.....	953	670	284	69	49	21	30	57	4.2	8.55	657	794	110	19	0.250	81.5	0.549	0.398	0.057	0.465	0.012	0.092	73	10	83	2.2	15
20[1]	16/12	6.00	9/25	Dysentery; slight dehydration for 1 week; not very sick.....	...	...	...	..	..	..	35	..	...	8.61	648	788	105	22	0.240	78.4	0.662	0.378	0.067	0.445	0.012	0.205	57	10	67	1.8	31
20[2]	16/12	6.03	9/29	Same; better	405	268	137	67	45	23	34	20	3.3	7.43	657	771	...	..	.....	....	0.523	.....	.....	.....	.....	.....	..	..	..	...	..
21[1]	2	10.67	10/ 1	Dysentery; very sick and dehydrated for 1 week...	...	...	...	..	..	..	29	..	...	7.48	570	670	105	7	0.216	92.2	0.702	0.379	0.022	0.401	0.010	0.291	54	3	57	1.4	42
21[2]	2	10.00	10/ 8	Same; still dehydrated....	931	660	271	93	66	27	29	49	4.9	7.37	562	671	92	18	0.202	79.5	0.478	0.327	0.054	0.381	0.010	0.087	68	11	79	2.1	18
22	8/12	5.50	4/10	Vomiting; diarrhea; very sick and dehydrated for 3 days	355	260	78	64	46	14	27	21	3.8	7.96	755	915	107	38	0.267	68.3	0.625	0.384	0.113	0.497	0.011	0.117	61	18	79	1.7	19
23	1/12	....	5/ 1	Otitis media; dehydration; not very ill for 3 days...	...	...	...	..	..	..	26	..	...	8.61	736	908	...	..	.....	....	0.704	.....	.....	.....	.....	.....	..	..	..	...	..
24	6/12	6.30	10/11	Otitis media; diarrhea, very ill and dehydrated for 4 days.....	...	...	...	..	..	..	..	..	...	8.73	572	707	...	..	.....	....	0.705	.....	.....	.....	.....	.....	..	..	..	..	..
25	6/12	6.05	5/30	Otitis media; diarrhea and dehydrated for 1 week...	...	...	...	..	..	..	..	..	...	6.90	659	777	...	..	.....	....	0.556	.....	.....	.....	.....	.....	..	..	..	...	..
26	2/12	3.66	8/17	Anemia; diarrhea and vomiting, dehydration for 1 week	156	128	28	43	35	8	18	12	3.2	9.13	650	794	...	..	.....	....	0.549	.....	.....	.....	.....	.....	..	..	..	...	..
27	6/12	4.66	10/10	Diarrhea; vomiting, acidosis; blood taken 4 hours before death	...	...	...	..	..	..	35	..	...	8.73	641	801	119	14	0.252	87.0	0.554	0.426	0.042	0.468	0.012	0.074	77	8	75	2.2	13
28	9/12	....	5/ 7	Pyelitis; vomiting and dehydration for 1 week....	...	...	...	..	..	..	28	..	...	7.90	580	720	90	25	0.214	73.1	0.558	0.322	0.076	0.398	0.011	0.149	58	14	72	2.0	27
32	6/12	4.15	9/22	Otitis media; diarrhea and dehydration for 1 week..	...	...	...	..	..	..	34	..	...	8.02	597	711	103	14	0.222	85.3	0.534	0.372	0.041	0.413	0.011	0.110	70	8	78	2.1	21
33	1	6.60	9/10	Undernutrition and dehydration	418	288	130	63	44	20	31	..	...	....	...	...	102	..	.....	....	.....	.....	.....	.....	.....	.....	..	..	..	..	..
34	1	10.90	8/ 6	Convalescent from dysentery; not clinically dehydrated	850	546	310	78	50	29	37	43	3.9	7.90	585	680	101	12	0.200	86.5	0.502	0.352	0.036	0.388	0.011	0.103	70	7	77	2.2	20
35[1]	16/12	5.61	12/ 6	Celiac disease; vomiting; diarrhea and dehydration 1 week.....	455	320	135	81	57	24	30	29	5.9	9.07	573	716	103	15	0.222	84.0	0.500	0.339	0.045	0.414	0.013	0.163	63	8	71	2.2	28
35[2]	16/12	6.53	12/15	Same; better	558	360	198	85	55	30	35	28	4.4	7.90	581	700	104	12	0.220	87.0	0.500	0.374	0.035	0.409	0.011	0.170	63	6	69	1.9	29
35[3]	19/12	6.65	2/ 2	Same; gaining slowly.....	452	345	107	68	52	16	24	30	4.5	8.73	587	724	99	19	0.218	80.0	0.733	0.356	0.051	0.407	0.012	0.304	49	7	56	1.6	42

TABLE 4.—*Data of Patients with Water Retention or a Tendency to Water Retention*

Clinical Notes					Volume of Blood						Concentration of Red Blood Cells and Serum Protein				Concentration of Electrolytes of Serum						Concentration of Crystalloids in Terms of Freezing Point									
Case	Age in Years	Weight in Kg.	Date	Clinical Manifestations	Blood, Cc.	Plasma, Cc.	Cells, Cc.	Blood, Cc. per Kg.	Plasma, Cc. per Kg.	Cells, Cc. per Kg.	Red Blood Cells, % by Volume	Serum Protein, Gm.	Serum Protein, Gm. per Kg.	Serum Protein, %	Conductivity of Serum	Corrected Conductivity	Chlorides, Millimols	Bicarbonates, Millimols	Osmolar Concentration of electrolytes	% of Electrolytes as Chlorides	Freezing Point, Degrees	Part by Sodium Chloride	Part by Sodium Bicarbonate	Part by Electrolytes	Part by Proteins	Part Not Accounted for	% by Sodium Chloride	% by Sodium Bicarbonate	% by Electrolytes	% by Proteins	% Not Accounted for
36[1]	2.5	15.85	7/23	Lipoid nephrosis, anasarca and ascites	...	...	...	..	..	..	..	..	...	5.59	685	778	...	..	.....	..	0.500	.....	.....	.....	.....	.....	..	..	..	..
36[2]	2.75	15.10	9/25	Same; cholesterol, 700 mg.; marked edema	649	465	184	40	31	13	28	32	2.2	7.09	600	700	...	..	.....	..	.....	.....	.....	.....	.....	.....	..	..	..	..
36[3]	2.8	15.40	10/21	Same; cholesterol, 350 mg.; marked edema	...	...	...	..	..	..	..	..	...	7.09	540	640	...	..	.....	..	0.525	.....	.....	.....	.....	.....	..	..	..	..
36[4]	2.8	15.56	10/23	Same; cholesterol, 247; moderate edema	...	...	...	..	..	..	27	..	...	7.84	...	...	...	..	.....	..	.....	.....	.....	.....	.....	.....	..	..	..	..
36[5]	3	15.02	1/ 9	Same; marked edema	609	410	199	41	27	12	33	30	2.0	7.37	537	642	...	..	.....	..	0.562	.....	.....	.....	.....	.....	..	..	..	..
36[6]	3	15.15	1/15	Same; blood cholesterol 247; marked edema	614	430	184	41	29	12	30	39	2.3	7.9	...	...	...	..	.....	..	.....	.....	.....	.....	.....	.....	..	..	..	..
36[7]	3.25	14.54	5/13	Same; no visible edema	1054	724	330	73	50	23	31	62	4.3	8.55	552	681	...	..	.....	..	0.646	.....	.....	.....	.....	.....	..	..	..	..
37[1]	9	33.0	3/ 9	Lipoid nephrosis; anasarca; ascites	2080	880	1200	63	27	36	58	56	2.0	6.34	...	...	...	..	.....	..	.....	.....	.....	.....	.....	.....	..	..	..	..
37[2]	9.1	31.0	4/22	Same; slight edema	2437	1231	1206	79	40	39	50	74	2.4	5.99	651	734	106	15	0.228	85	.....	0.381	0.045	0.426	0.009	.....	..	..	..	..
37[3]	9.2	27.7	5/ 4	Same; no visible edema	2600	1320	1280	94	48	46	49	84	3.0	6.39	624	735	...	..	.....	..	.....	.....	.....	.....	.....	.....	..	..	..	..
38	39	60.9	4/ 4	Chronic nephrosis with slight edema	4200	2605	1595	69	41	26	38	166	2.7	6.34	...	...	...	..	.....	..	0.610	.....	.....	.....	.....	.....	..	..	..	..
39[1]	11	40.45	10/ 2	Subacute nephritis with edema; nonprotein nitrogen, 115 mg.; cholesterol, 186	2252	1500	752	56	37	19	34	100	2.5	6.62	560	672	104	9	0.214	90	0.640	0.372	0.026	0.398	0.009	0.232	58	4	62	1.4	37
39[2]	11	39.77	12/18	Same with pneumonia; receiving 100 cc. fifth normal hydrochloric acid	1586	1182	404	40	30	10	26	74	1.9	6.22	...	...	108	..	.....	..	.....	0.391	.....	.....	0.009	.....	..	..	..	..
40	3	15.45	5/14	Convalescent acute hemorrhagic nephritis	1050	763	287	68	49	19	27	71	4.6	9.37	652	821	102	30	0.245	73	0.604	0.367	0.089	0.456	0.013	0.135	61	15	76	2.1	21
41	11	36.35	2/ 2	Convalescent acute hemorrhagic nephritis; nonprotein nitrogen, 35	...	...	...	..	..	..	28	..	...	7.61	550	662	109	3	0.216	97	0.683	0.395	0.007	0.402	0.011	0.271	58	1	59	1.5	40
42[1]	12	36.35	3/13	Chronic nephritis with hypertension	3125	2172	953	86	60	26	31	142	3.9	6.57	...	...	103	..	.....	..	.....	0.369	.....	.....	0.009	.....	..	..	..	..
42[2]	12	35.90	3/15	Same; nonprotein nitrogen, 41; plasma cholesterol, 189	3250	2100	1150	91	59	32	35	138	3.8	6.57	522	610	...	..	.....	..	0.545	.....	.....	.....	.....	.....	..	..	..	..
43[1]	6	21.25	1/29	Lobar pneumonia	1352	884	468	64	42	22	35	76	3.6	8.61	643	793	84	40	0.225	62	0.547	0.301	0.117	0.418	0.012	0.117	55	22	77	2.4	21
43[2]	6	17.72	2/ 5	Same; after crisis	1330	820	510	75	46	29	38	63	3.6	7.67	550	661	...	..	.....	..	0.503	.....	.....	.....	.....	.....	..	..	..	..
44	9.5	23.64	5/16	Lobar pneumonia	1523	997	585	65	40	25	39	81	3.4	8.6	680	836	...	..	.....	..	0.500	.....	.....	.....	.....	.....	..	..	..	..
45	1.3	11.0	4/10	Convalescent lobar pneumonia	819	500	319	74	45	29	39	38	3.5	7.61	640	766	97	26	0.228	74	0.558	0.347	0.078	0.415	0.011	0.122	60	14	74	1.8	22
46	4	14.1	5/19	Convalescent lobar pneumonia	...	...	...	..	..	..	..	..	...	8.46	597	733	...	..	.....	..	0.475	.....	.....	.....	.....	.....	..	..	..	..

a value of 0.022 C. for a 6.4 per cent solution of egg albumin, which would amount to a depression of 0.00344 C. for a 1 per cent solution.

The considerable fraction of the freezing point depression, unaccounted for by electrolytes or proteins, is presumably due to the presence of organic crystalloids in considerable quantity but obviously cannot be accounted for, under ordinary circumstances, by urea, sugar and cholesterol. Thus, for example, a solution containing in 100 cc., 100 mg. of dextrose, 30 mg. of urea and 150 mg. of cholesterol would have an estimated freezing point depression of about 0.0264 C., which is considerably less than the difference observed in any of our cases between the total freezing point depression and that fraction due to electrolytes and proteins.[24]

It is realized, of course, that one cannot obtain a highly accurate correction for the influence of serum protein concentration on conductivity (Atchley et al[25]).

COMMENT

Determinations of the blood volume of normal infants have been reported by Lucas and Dearing [26] and by Bakwin and Rivkin [27] and on athreptic infants by Marriott [6] and by Bakwin and Rivkin.[27] The values here shown for undernourished infants agree with those of Bakwin and Rivkin and Marriott. The results obtained by Lucas and Dearing are somewhat higher, due perhaps, to a difference in technic. It is important to bear in mind, as shown by numerous investigators working with both infants and adults, that the plasma volume in terms of cubic centimeters of plasma per kilogram of body weight tends to remain constant, variations in the total blood volume being largely due, especially in anemic

24. As pointed out by Van Slyke, Wu and McLean (J. Biol. Chem. **56**:765, 1923), the protein in a solution such as serum occupies space. The quantity of water in 100 cc. measured by volume can be calculated according to the question $99 - 0.8\ p = x$ in which x is the percentage of water and p is the percentage of protein. Thus, if the concentration of serum protein is 7 per cent the actual water would amount to only 93.4 per cent of the measured volume. If this correction were applied to our results, the effect would be to increase somewhat the fraction of the freezing point depression due to electrolytes and to reduce the fraction which is not accounted for. Actually the fraction of the freezing point depression which is unaccounted for would be reduced from 5 to 8 per cent. But even this correction would not explain the discrepancy here noted.

25. Atchley, D.; Loeb, R.; Benediet, E., and Palmer, W.: Physical Properties and Chemical Studies on Human Serum, Arch. Int. Med. **31**:606 (April) 1923. However, since the chief factor that affects the accuracy of the correction is the hydrogen ion concentration, we believe that for our purposes the correction of Gram and Cullen [17] is trustworthy. That is, we feel reasonably sure that, in a given instance, a high value for the fraction, sodium chloride concentration determined by analysis divided by sodium chloride concentration calculated from the conductivity value, means a really low concentration of other electrolytes, notably sodium bicarbonate; and vice versa.

26. Lucas, W. P., and Dearing, B. I.: Blood Volumes in Infants Estimated by the Vital Dye Method, Am. J. Dis. Child. **21**:96 (Jan.) 1921.

27. Bakwin, H., and Rivkin, H.: Estimation of the Volume of Blood in Normal Infants and Infants with Severe Undernutrition, Am. J. Dis. Child. **27**: 340 (April) 1924.

and undernourished infants, to variations in the volume of red corpuscles. As shown by Bock,[28] the value for adults is about 50 cc. of plasma per kilogram of body weight. According to Bakwin and Rivkin,[27] Lucas and Dearing,[26] Marriott [6] and our own investigations,[29] this value is somewhat greater and more variable during the first three years of life, lying perhaps between 55 and 65 cc. of plasma per kilogram of body weight. The variability of the plasma volume in terms of body weight in early life, however, is too great to permit the drawing of conclusions in individual cases by comparing the plasma volume in a given case with the mean normal value. We have, therefore, whenever possible, made comparisons of successive determinations in a given case. That is to say, except in extreme cases, the accuracy of the method for the determination of plasma volume is probably greater than the constancy of the plasma volume.

It is evident from the patients here presented that those not showing clinical evidence of dehydration or water retention, and in whom such dehydration or water retention would not be expected, show a plasma volume per kilogram of body weight of 50 cc. or over. On the other hand, with the exception of the infant with celiac disease (case 35), all of the nine infants showing clinical evidence of dehydration showed diminution of the plasma volume distinctly below 50 cc. per kilogram of body weight. This is evinced not merely by single determinations in individual cases, but especially by those cases in which from multiple determinations the total plasma volume is seen to rise with disappearance of the dehydration.

Thus the infant in case 16 showed 200 cc. of plasma (40 cc. per kilogram of body weight) while dehydrated, and 340 cc. (62 cc. per kilogram of body weight) after recovery only four days later. This was a typical case of diarrhea and dehydration in a malnourished infant. The patient in case 17 showed 446 cc. of plasma (39 cc. per kilogram of body weight) when dehydrated, and 570 cc. (50 cc. per kilogram of body weight) after recovery. This child had encephalitis and became dehydrated from lack of fluid intake. The infant in case 18 showed 276 cc. of plasma (43 cc. per kilogram of body weight) when dehydrated, and 434 cc. (62 cc. per kilogram of body weight) after recovery a week later. This child, though well nourished, had an acute form of vomiting, diarrhea and dehydration. The child with lead encephalitis (case 19) had dehydration brought on by lack of fluid intake and showed an increase from 477 cc. of plasma (40 cc. per kilogram of body weight) to 677 cc. (51 cc. per kilogram of body weight). A patient with celiac disease (case 35) showed 320 cc. of plasma when dehydrated and 360 cc. after recovery from the dehydration. This is the only patient studied who did not show an increase in the plasma volume per kilogram of body weight on recovery from dehydration. The volume was slightly lower during dehydra-

28. Bock, A. V.: The Constancy of the Plasma Volume, Arch. Int. Med. **27:** 83 (Jan.) 1921.

29. Darrow, D. C.; Soule, H. C., and Buckman, T. E.: Blood Volume in Normal Infants and Children, J. Clin. Investigation **5:**243, 1928.

tion, but apparently the tissues had lost considerably more water than the blood as the weight increased 20 per cent with recovery, while the plasma volume increased only an insignificant amount. In all the other patients on whom two determinations were made, the plasma was more dehydrated than the tissues, as can be seen by inspecting the values for the weights and plasma volumes. The greatest loss of water from the plasma (35 cc. per kilogram of body weight) was observed in an infant (case 26) aged 2 months, with a severe anemia brought on by umbilical sepsis and osteomyelitis. This patient did not respond to intravenous injection of dextrose solution, but did recover almost immediately after a blood transfusion. Apparently a minimum volume of red cells is necessary to maintain the blood volume, as was pointed out by Keith [30] and Robertson and Bock.[31] That is, in patients with anemia, blood transfusion is indicated for its effect on the water carrying function of the blood as well as on the gas carrying function.

The plasma volume was also definitely diminished in the infants with long standing retention of water (chronic nephrosis, subacute nephritis) whom we studied.

The return of the plasma volume to normal, with disappearance of edema, is clearly indicated in cases 36 and 37. In case 36 the child showed a persistently low plasma volume for three and a half months, as indicated by three determinations (465 cc., 410 cc. and 430 cc.); then, after a short period of recovery which took place four months later, the plasma volume rose to 724 cc. In case 37, the child showed an increase from 880 cc. of plasma to 1,320 cc. in a period of six weeks. The adult in case 38 showed only a slight decrease, but the child in case 39 had a plasma volume of only 30 cc. per kilogram of body weight a short time before death from chronic nephritis with edema, complicated by pneumonia. The nonedematous nephritic patients did not show a change in the plasma volume. A separate study of the blood volume in fever and pneumonia was made and reported elsewhere.[32] In that paper it was shown that the plasma volume is usually increased slightly in febrile patients including children with primary pneumonia, but the increase is usually masked by the storage of water diffusely throughout the body. The cases reported here do not show this, however.

Diminution in the plasma volume is direct evidence of serious embarrassment of the water metabolism of the body. In view of the relatively constant volume in normal persons and in many pathologic states, the considerable diminution reported here, both in states of dehydration and in retention of water, is surprising. The question remains now of determining whether this diminution of the plasma volume is a simple dehydration of the plasma, or whether the concentration of the plasma is

30. Keith, N. M.: Blood Volume in Wound Shock and Primary Hemorrhages, Special Report, National Health Ins. Med. Res. Com., Series nos. 26 and 27, London, 1919.

31. Robertson, O. H., and Bock, A. V.: Blood Volume in Wounded Soldiers, J. Exper. Med., vol. 19, pp. 139 and 155.

32. Soule, H. C.; Buckman, T. E., and Darrow, D. C.: Blood Volume in Fever, J. Clin. Investigation **5**:229, 1928.

maintained relatively constant in spite of the changes in plasma volume. The following analysis of our results was undertaken in an attempt to answer this question.

ANALYSIS OF RESULTS

Red Cells.—Since, as shown by Bock [28] and by Buckman, Ohler and Doherty,[33] extreme variations in the volume of red corpuscles are compatible with a normal plasma volume in chronic anemia and chronic polycythemia, a single determination of the percentage volume of red cells cannot be used as evidence of blood concentration in any but the most acute cases. Furthermore, it is well known that the body can make new erythrocytes rapidly under favorable circumstances. It does not, therefore, seem likely that the percentage volume of red corpuscles will reflect the change in the plasma volume if the determinations are done after the lapse of more than one or two weeks. This fact is brought out by the four infants with dehydration on whom multiple determinations were made (cases 16, 17, 19 and 35). In case 16, the infant showed diminishing concentration of the red corpuscles with increasing plasma volume, as one would expect. However, the change in cell volume is not sufficiently great to account for the change in plasma volume. One must assume either that the first sample of venous blood showed a lower concentration of red cells than the rest of the blood, due, perhaps, to piling up of the corpuscles in the capillaries, or that with recovery new erythrocytes were formed, or that there occurred a release of erythrocytes stored in the spleen or elsewhere. The determinations in case 17 were six weeks apart, so that a correspondence was not found nor was one expected. The percentage volumes in case 19 reflect the changes in plasma volume in the last three determinations, which were all made after recovery from dehydration. However, a correspondence is not to be expected between the determination made while the patient was dehydrated and the next one, done a month later on account of removal of the patient from the hospital because of chickenpox. In the infant with celiac disease (case 35), the first two determinations were nine days apart, and although the plasma volume increased slightly from 320 to 360 cc., the percentage volume of red cells also increased from 30 to 35 per cent. The increased total volume of red cells in this case, as in case 16, may have two interpretations. The third determination is not comparable with the preceding one on account of the lapse of six weeks. In cases 20 and 21, the plasma volumes were not determined at the time of the first observation; but whatever fluctuations in the plasma volumes may have occurred, it is obvious, from the values for the percentage volumes of the red cells taken at the height of the dehydration and after improvement, that the concentration of the red corpuscles did not change. Thus, in dehydration a rough indication of the fluctuations of the plasma volume may be given by the values of the percentage volume of red cells, but the indication is not at all quantitative and after from one to two weeks it is entirely unreliable.

Similarly, in the children showing evidence of retention of water, an apparent consistency did not exist in the fluctuations in the plasma volumes and the values for the percentage volume of red cells. In the children in whom determinations were separated by more than two weeks (cases 36, 37, 39 and 43), the red cell concentration did not measure the change in plasma volume except in case 37.

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33. Buckman, T. E.; Ohler, W. R., and Doherty, L. L.: The Electrolyte Content of the Red Blood Corpuscles. The Findings in Chronic Anemia and Polycythemia, J. M. Res. **44**:51, 1923.

In case 39, the patient was extremely sick and died of pneumonia and chronic nephritis with edema a few days after the last determination. He might have been expected to show such a progressive anemia as the determinations of the blood volume indicate. The children in cases 42 and 43 showed changes in the corpuscular volume greater than the change in the plasma volume even though the determinations were done within three and seven days, respectively. In case 13, the infant showed a fairly large change in the plasma volume in two determinations done two weeks apart and a corresponding change in the percentage volume of the red cells. Thus, though the red cell volume changes with the plasma volume, other factors besides the amount of circulating plasma seem to come into play to shift the concentration of the red cells.

Moreover, there seems not to be a parallelism between the percentage volume of red cells and the concentration of the electrolytes or the freezing point of the serum. In a certain number of cases, in a general way there appeared to be a parallelism between the percentage volume of red cells and the percentage of serum protein (cases 15, 16, 17, 36, 37 and 39), but in other cases a correspondence between the values was not found.

Apparently the body is able to withdraw red corpuscles from and return them to the blood in cases in which compensation has occurred in numbers which vary within wide limits without reference to the plasma volume. As far as the concentration of red cells is concerned, there is no indication of simple dehydration of the blood either in edema or in dehydration. The absolute volume of red cells, however, as would be expected, generally increases with the improvement of the patient's condition. It should be pointed out that the cases here presented are not comparable with those acute cases in which there is a sudden diminuation of plasma volume (hemorrhage, acute dehydration).

Serum Protein.—In the cases here reported, in which the infants were either dehydrated or edematous, the serum protein showed more consistent variation than the percentage volume of the red cells. Moreover, as the serum protein concentration is less prone than the concentration of red corpuscles to show variations in disturbances, not accompanied by changes in the plasma volume, it is perhaps fair to compare single determinations in different cases. It should be noted, however, that in three of our cases in which an elevation of the percentage of serum protein would not be expected, high values actually did occur (in case 5, one of undernutrition, the infant showed 9.06 per cent; the infant in case 13, convalescent from tetany, showed 8.55 per cent; in case 15, one of congenital hemolytic jaundice, the infant showed 8.90 per cent). In none of these cases was there a diminution of plasma volume; in none was there clinical evidence of dehydration; and in none was there obtained a history of diarrhea, vomiting, toxemia or other disturbance usually associated with dehydration.

As is the case with the total quantity of red corpuscles, so with the total quantity of serum protein, there is observed in practically all of those cases in which multiple determinations were done an increase in the total serum protein of the circulating blood concomitant with the rise in the volume of the plasma and clinical improvement, as though during the period of oligemia there had occurred a withdrawal or destruction of plasma protein, and an actual increase or reappearance with clinical improvement. The diminution in plasma protein is, however, by no means strictly parallel to the diminution in plasma volume. Nevertheless, in a general way, the loss in plasma protein is less than would be expected on the basis of a simple diminution of the plasma volume in the infants with dehydration, and greater in those with retention of water, so that in general the infants with the former condition tend to show a percentage of serum protein

above the normal and many of those with the latter condition tend to show a diminution of concentration of serum protein. This relationship is readily demonstrated by comparing the grams of protein per kilogram of body weight with the cubic centimeters of plasma per kilogram of body weight.

The determination of serum protein, therefore, is not an entirely reliable method for determining quantitatively the degree of desiccation of the blood, or even qualitatively of establishing the fact of a dehydrated condition of the blood or tissues.

The Concentration of Electrolytes.—Unlike the freezing point, the conductivity of the plasma does not have a known physiologic significance, and, in the present work, conductivity values were used to measure the total electrolyte concentration and indirectly to obtain some idea of the concentration of sodium bicarbonate in the serum. The serum conductivity values here reported show much greater fluctuations than the reported values for adults (Buckman et al.[33]). Moreover, our results are not in agreement with those of Berend and Tezner,[5] who obtained, in persons with dehydration, a slightly higher conductivity for the serum than normal. However, it is possible that dehydration was less acute in our infants than in those described by these investigators. The fluctuations observed in our cases are apparently unrelated to changes in the serum protein content or the volume of the plasma. The relationship of conductivity values to the freezing point values will be discussed later in the paper.

It is here assumed that the electrical conductivity values are made up exclusively of sodium chloride and sodium bicarbonate. From direct determinations of the sodium chloride content of the plasma (chloride ion expressed as sodium chloride), it is evident from the tables that the concentration of this electrolyte is maintained nearly constant at a value of about 104 millimols per liter. Three fourths of all the determinations show less than 5 per cent deviation from this mean value. In only four instances were distinctly low values obtained. Two of these occurred in patients with lobar pneumonia. One occurred in a patient with dysentery, and one, in a patient with pyelitis accompanied by vomiting. The infants with pneumonia showed a tendency to retention of water; the others showed a definite dehydration. In only three instances were distinctly high values obtained (case 17, 119 mm.; case 27, 119 mm., and case 19, 129 mm.). In case 17, the child had encephalitis; he was very ill at the time of observation and was clinically dehydrated. In case 27, the specimen of blood was obtained only four hours before death with symptoms of acute dehydration and intoxication. In case 19 the high value (corresponding to 754 mg. of sodium chloride per hundred cc. of plasma) can be accounted for on the basis of the therapeutic administration of 600 ml. of fifth-normal hydrochloric acid.[34]

Since quantitatively sodium chloride is overwhelmingly the most important electrolyte of the plasma, and since it is generally maintained at an almost con-

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34. We do not wish to imply that we think that variations in the sodium chloride content of the plasma may not be considerable and that these variations are not important. Especially significant in this connection is the recent work of Boyd, Courtney and MacLachlan (Metabolism of Salts in Nephritis: III. Chlorides and Sodium, Am. J. Dis. Child. **34**:218 [Aug.] 1927) in which it is shown that there is a definite retention of sodium and chlorine, as measured by balance experiments in the nephritis of childhood, and that this retention is associated, generally, with some elevation of the plasma chlorides. The points that we wish to make are, rather, that the body tends to maintain a constant level of plasma chloride and that the changes which do occur are not commensurate either in magnitude or direction with these changes in plasma volume.

stant level, the values for conductivity are also maintained at a fairly constant level, the variations being largely due to variations in the concentration of other electrolytes, notably sodium bicarbonate, except in those few cases in which the sodium chloride is markedly increased without compensatory diminution in the bicarbonate content.

Since the mean value of the sodium bicarbonate content of the arterial true plasma of a healthy, resting adult is nearly 20 millimols per liter, it may be assumed that values markedly lower than this, 10 or less, indicate diminution of bicarbonate content of the plasma. Such low values were encountered in cases 4, 13, 16, 19, 21, 39 and 41. As would be expected from the foregoing discussion, these are precisely the cases showing low conductivity values, except case 19 in which the administration of large quantities of hydrochloric acid not only reduced the bicarbonate content of the plasma to a minimum but raised the sodium chloride content to an excessively high level presumably by calling forth base from the tissues. (This patient had lead encephalitis and had been given a large quantity of hydrochloric acid for therapeutic purposes.) The patient in case 13, who had tetany, also received treatment with hydrochloric acid although evidently not enough to elevate the sodium chloride, and hence the conductivity values. The infants in cases 16 and 21 were severely ill with dehydration for more than a week. In cases 39 and 41, the children had acute nephritis. Case 4 was that of a markedly undernourished infant, not otherwise remarkable clinically. It is interesting to note that in all of these infants with low sodium bicarbonate content except the two (19_2 and 13_2) to whom hydrochloric acid was given, the fraction of the freezing point depression value unaccounted for by electrolytes and serum protein was distinctly elevated, though these are not the only cases in which this occurred; that is to say, with the exceptions already noted, the patients with low conductivity values show also low values for sodium bicarbonate and high values for what inferentially must be looked on as organic nonelectrolytes. Conceivably the organic substances may be certain organic acids that may influence the freezing point depression more than the conductivity. More likely this unaccounted for fraction is due to nonprotein nitrogenous constituents which, as Schloss [35] and Schwartz and Kohn [36] have shown, may be much increased in dehydration.

Concerning the high values for sodium bicarbonate, inference cannot be drawn, because in these cases the bicarbonate content of the venous blood was not determined directly, and the extent of the chloride ion transfer from corpuscles to plasma on exposure to air is not known. It is a little surprising, however, to find such high values in the patients with pneumonia who ordinarily show low values for the bicarbonate content of the venous true plasma.

The Freezing Point of the Plasma.—Salge [2] reported an average freezing point of —0.541 C. in normal and undernourished children and an average value of —0.63 C. in cases of "intoxication." In the series of cases here reported, the values for the freezing points of the serum fall largely between —0.51 and —0.6 C. In about two thirds of the cases, the values lie between —0.51 and —0.58 C. These values are generally not in agreement with Salge's and are definitely lower than the values generally reported for adults. In agreement with Salge, we find a tendency to a slight increase in the magnitude of the freezing point depression in the most acute cases of dehydration.

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35. Schloss, O. M.: Intestinal Intoxication in Infants; the Importance of Impaired Renal Function, Am. J. Dis. Child. **15**:165 (March) 1918.

36. Schwartz, H., and Kohn, J. L.: Toxic Symptoms in Infants and Children with Gastro-Intestinal Manifestations, Am. J. Dis. Child. **21**:465 (May) 1921.

It is obvious from inspection of the tables that a simple relation does not exist between plasma volume and freezing point, or between retention of water or dehydration and the freezing point of serum, except possibly in the most acute cases of dehydration. Of fifteen instances in which a low plasma volume was demonstrated and in which determination of the freezing point was made, the freezing point of the serum was found to be below —0.58 C. in only four. On the other hand, in only half of the eighteen instances in which the freezing point of the serum was less than —0.58 C. was the plasma volume found to be abnormally low.

Moreover, it is clear that a relation does not exist between the concentration of serum protein or of red corpuscles and the freezing point of the serum. The relation of freezing point of the serum to the concentration of electrolytes is described later in the paper.

In order properly to evaluate the significance of the freezing point, it is necessary to bear in mind that the freezing point of the serum is influenced: first, by the concentration of electrolytes, especially sodium chloride and sodium bicarbonate; secondly, and to a variable extent, by organic crystalloids (for example, urea and other nonprotein nitrogenous substances, sugar, cholesterol, etc.); and thirdly, and to a slight extent, the proteins of the plasma. As illustrated by the values reported in the tables, the freezing point of the plasma varies within narrow limits because of the presence of a large and relatively constant quantity of a highly dissociated substance of low molecular weight, sodium chloride. In eleven of the eighteen instances in which the freezing point depression was slightly to moderately increased, greater than 0.58 C., simultaneous determinations of the concentration of electrolytes were made (cases 17, 19_2, 20_1, 21_1, 22, 35_1, 35_2, 35_3, 39_1, 40 and 41). In two instances, 17 and 22, the concentrations of electrolytes as well as organic crystalloids are definitely increased; in the other instances the increase in the magnitude of the freezing point depression is largely accounted for by an increase in the concentration of organic crystalloids. Generally speaking, values for freezing points of the serum above about —0.61 C. are largely dependent on the electrolyte content, but values for freezing points below about —0.61 C. are influenced greatly by the concentration of nonelectrolytes.

These facts call for brief comment. It is known that the sodium bicarbonate content of the blood may be altered, for example, in respect to the rate of the pulmonary ventilation. Moreover, the carbon dioxide tension to which the blood is exposed alters somewhat the distribution of chloride ions between plasma and cells, high tensions or carbon dioxide tending to decrease the chloride ion content of the plasma. It is likely that the same reaction occurs in the tissues, so that a competition exists between the blood and the tissues for bicarbonate, sodium chloride and water. If this is true, the concentration of these electrolytes in the plasma will depend not only on simple diffusion but on such factors as basal metabolic rate, rate of blood flow and efficiency of pulmonary ventilation. On the other hand, as far as is known, such a competition does not exist in the case of the organic crystalloids, so that variations in the concentration of these substances represent presumably either derangements of the metabolism or renal disturbance or a true concentration of the tissue fluids and the plasma. What is needed is more information concerning the rate of blood flow, the rate of carbon dioxide production in the tissues and the influence of these factors in a given case on the capacity of the blood to absorb water as it passes from an arterial to a venous environment.

One thing is clear: diminution of plasma volume is rarely accompanied by a simple concentration of crystalloids. To a much greater extent even than is the

case with the red corpuscles or serum protein, the body tends to maintain the concentration of plasma crystalloids at a constant level, and the variations that occur are largely controlled by other factors than change of the plasma volume.

From this analysis of the data obtained in these cases, it is evident that the diminution of plasma volume observed in infants showing dehydration and those showing retention of water is not accompanied by a simple dehydration of the blood. These infants do not show, therefore, anhydremia but, rather, oligemia. That is, electrolytes and crystalloids leave the blood in amounts approximately proportional to the loss of the water from the blood.

SUMMARY

1. In a series of ten cases showing evidence of dehydration, the volume of plasma in terms of cubic centimeters of plasma per kilogram of body weight was reduced definitely below normal in nine. In four of the five cases in which multiple determinations were made, there occurred, with clinical improvement, a marked increase in the absolute plasma volume, and the volume of plasma in cubic centimeters per kilogram of body weight returned to the normal level. Similarly, in seven of eight cases showing evidence of retention of water there was a definite reduction in the plasma volume in terms of cubic centimeters of plasma per kilogram of body weight. In those cases, three in number, in which the plasma volume was determined during the period of retention and after all evidence of retention had disappeared, a marked increase in the absolute plasma volume occurred with improvement, and the volume of the plasma in cubic centimeters per kilogram also increased to the normal value.

2. Although in all of those cases in which multiple determinations were made the absolute volume of red corpuscles tended to increase with increase in the plasma volume and improvement in the patient, it is certain that the variations were not proportional to changes in the plasma volume, and the change in concentration of the red cells did not reflect accurately the changes in the plasma volume.

3. There is a definite parallelism between the values for total grams of serum protein and the total plasma volume: an actual loss of serum protein occurs with diminution of plasma volume, protein being returned to the plasma during the period of restoration of its volume to normal. In cases showing retention of water, the loss of serum protein is proportionately greater than the loss in plasma volume, so that the concentration of protein is diminished. In cases showing dehydration, the loss of serum protein is, generally, proportionately less than the loss of plasma volume, so that these cases show an increased concentration of serum protein. Variations from this general rule are often great, and the serum protein concentration is not a trustworthy index of dehydration or water retention, or of changes in blood volume.

4. The chloride ion concentration of the serum in the cases here reported is quite unaffected by changes in plasma volume and tends to be maintained at a level of about 104 millimols. The relatively high concentration of sodium chloride and its low molecular weight and high degree of dissociation make this substance the most influential factor in regulating the electrical conductivity and freezing point of the plasma. The almost constant level at which the sodium chloride concentration is maintained tends to prevent marked variations in the electrical conductivity and freezing point depression. The variations in conductivity are due largely to variations in electrolytes other than sodium chloride, notably sodium bicarbonate. Although the true bicarbonate content of the plasma may have an important bearing on the mechanism controlling the volume and concentration of the plasma, values presumably representing the content of residual bicarbonate of the serum do not bear a relation to plasma volume or the concentration of other substances in the plasma.

5. In the great majority of cases here reported, the freezing point of the serum lies between —0.51 and —0.6 C., values somewhat lower and somewhat more variable than those reported for adults. The values for total freezing point depression vary independently of plasma volume or serum protein concentration. After quantitites representing the depression due to electrolytes and serum protein are subtracted from the total values for freezing point depression, there remains a fraction amounting to from about 20 to 40 per cent of the total value. This fraction presumably represents organic crystalloids. Variations in values for freezing point depression between —0.51 and —0.58 per cent C. are largely due to variations in the electrolyte concentration, but depression of the freezing point below 0.58 C. is generally due to an increase in the concentration of organic crystalloids. A simultaneous increase in electrolytes and organic crystalloids rarely occurs.

Generally speaking, the body is able to maintain the concentration of electrolytes and organic crystalloids at values which vary within relatively narrow limits. In those few instances in which there occurs an increase in the organic crystalloids in the presence of diminished plasma volume, it was impossible to determine whether the increase was due to an increased production, a faulty elimination or a dehydration of the plasma. The scanty urinary excretion in dehydration points to faulty elimination.

6. It is suggested that such factors as rate of blood flow, basal metabolic rate and the capacity of the blood to absorb water as it passes from arterial to venous surroundings may be important factors in determining the absorption of water from the gastro-intestinal tract in patients with dehydration, or from the tissues in patients with water retention.

CONCLUSIONS

1. In early life, diminution of the plasma volume occurs regularly in infants showing dehydration, and may occur in conditions in which there is a tendency to water retention. With clinical improvement, an increase of plasma volume occurs.

2. In subacute and chronic cases, at any rate, the diminution of plasma volume is not the result of a simple dehydration of the blood, and the condition should be termed oligemia rather than anhydremia; the concentration of crystalloids is only slightly affected by the change in plasma volume, and the variations in the concentration of serum protein and red corpuscles are not proportional to the changes in plasma volume.

FACTORS IN THE DECAY OF TEETH*

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In the annual inspection of the school children of Rochester, a high incidence of dental caries was found. This corresponds roughly to observations elsewhere in the northern states. In order to evaluate the possible etiologic factors, two groups of children were selected for comparison: twenty-five with perfect or nearly perfect teeth and twenty-five with marked dental caries. It seemed probable that the differences would be most striking if extremes were chosen.

ROUTINE EMPLOYED

In the inspection of the children in the Rochester public schools, the names were recorded of all who had exceptionally good or exceptionally poor teeth. In the first group were those whose teeth were free from caries and had not required dental work or had possibly two or three small fillings, and the enamel appeared smooth, hard and healthy, although not necessarily well cared for. In the second group were those whose teeth showed dental caries involving about half or more than half of the teeth. Children whose teeth showed the ridges and defective enamel recognized as due to definite nutritional disturbance were not included in these two groups. The ages of the children ranged from 5 to 13.

The mother of each child was questioned carefully with regard to the child's diet from birth, the condition and care of the teeth, the time of eruption, the amount of outdoor play, the general health and the past illnesses. She was also questioned with regard to her diet and health during pregnancy, the amount of sunshine and outdoor exercise, and dental trouble during that period. The condition of the teeth of both parents was ascertained by questioning and when possible by inspection.

As far as possible each factor was graded on the basis of 1 to 4. No selection of cases was made after the first listing of names, and the first twenty-five children from each list about whom satisfactory information was obtained were used to form the final groups. The data so obtained were incorporated into two charts, those of children with good teeth

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* Work done in Section on Pediatrics, Mayo Clinic.

(group 1, cases 1 to 25), and those with poor teeth (group 2, cases 26 to 50). Six typical cases from each group are shown in tables 1 and 2. A comparison of the two groups was made from the two charts, and the results are shown in table 3. The average age of the children was 9.5

TABLE 1.—*Observations on Children with Exceptionally Good Teeth (Six Cases, Group 1)*

	Case 1	Case 5	Case 19	Case 20	Case 16	Case 22
Age	6 years	10 years	13 years	11 years	9 years	11 years
Prenatal Period						
Health of mother	Not good	Very good	Good	Good	Good	Very good
Diet: Meat	±	+	+++	+	++	++
Potatoes	+	+	++	++	++	++
Green vegetables	++	+++	+++	+++	++	++
Fruits	++	+++	+++	++	++	+
Sweets	±	+	+	±	+	+
Milk	0	0	±	0	±	0
Outdoor exercise	+	++	+	+++	+	+
Dental trouble	++	+++	0	0	0	0
Heredity						
Caries of father's teeth	+	+++	0	++	+	+
Caries of mother's teeth	++	+++	0	0	+	0
First Year of Life						
General health	Good	Good	Good	Good	Good	Good
Breast-fed	6 mo.	6 mo.	9 mo.	9 mo.	12 mo.	9 mo.
Cow's milk or substitutes	Cow's milk	Cow's milk and lime water				
Cereal, when started	12 mo.	9 mo.	9 mo.	5 mo.	Occ. after 6 mo.	6 or 7 mo.
Vegetables, when started	12 mo.	9 mo.	9 mo.	6 mo.	12 mo.+	12 mo.+
Orange juice	++	++	0	+++	+	±
Cod liver oil	0	0	0	0	0	0
First teeth: Time of eruption	11 mo.	3 mo.	7 or 8 mo.	6 mo.	8 mo.	4 mo.
Condition	Good	Good	Very good	Good	Good	Good
Care	0	Boric	0	0	0	0
After First Year						
Diet: Milk	++	+	+	++	+++	0
Meat	±	++	±	+	0	++
Eggs	++	++	0	+	++	++
Green vegetables	+++	+++	±	++	++	++
Fruits	+++	+++	++	++	0	±
Cereals	++	0	+	+	++	+
Potatoes	++	+	+++	++	+++	+
Sweets	+	±	++	±	+	±
Candy	±	±	+	+	+	+
Teeth: Brushing	++	+	+	+	++	+
Dental care	1 filling	1 extraction	0	3 fillings	1 extraction	2 extractions
Diseases: Rickets	0	0	0	0	+	0
Scurvy	0	0	0	0	0	0
Convulsions	0	0	0	0	0	0
Measles at	6 yr.	4 yr.	2 yr.	3 yr.	2 yr.	2 yr.
Mumps at	0	6 yr.	0	5 yr.	0	0
Pertussis at	½ yr.	8 yr.	0	3 yr.	0	5 yr.
Chickenpox at	0	0	6 yr.	6 yr.	6 yr.	0
Scarlet fever	0	0	0	0	0	0
Diphtheria	0	0	0	0	0	0
Respiratory	±	±	±	±	±	±
Others	0	0	0	Ruptured appendix	Tonsillitis and earache till age of 5 years	0
Outdoor play	+++	+++	++	+++	+++	+
Comment	.....	Infant also has good teeth				

years in the first group and 6.1 years in the second. This raises the question whether the first teeth decay more readily than the second teeth, or whether the difference in age is accidental. Conclusions as to this cannot be drawn from this study.

TABLE 2.—*Observations on Children with Exceptionally Poor Teeth (Six Cases, Group 2)*

	Case 26	Case 29	Case 30	Case 31	Case 32	Case 45
Age	8 years	10 years	7 years	7 years	7 years	7 years
Prenatal Period						
Health of mother	Good	Good	Good	Good	Good	Not good
Diet: Meat	0	++	+++	++	+++	±
Potatoes	++	+++	+++	++	+++	++
Green vegetables	++	+++	+	++	+	+++
Fruits	++	++	+	+	+	++
Sweets	+	+	++	+	++	++
Milk	+	+	0	+	+++	0
Outdoor exercise	±	+	+++	+	++	+
Dental trouble	0	0	++	0	+++	0
Heredity						
Caries of father's teeth	++	+++	+	+	+++	++++
Caries of mother's teeth	0	+++	+++	++	++	++++
First Year of Life						
General health of child	Good	Good	Good	Good	A twin, never strong	Good
Breast fed	18 mo.	8 mo.	13 mo.	9½ mo.	13 mo.	12 mo.
Cow's milk or substitutes	.....	Cow's milk supplementing	With cow's milk after 9 mo.			
Cereal, when started	18 mo.	6 mo.	9 mo.	3 or 4 mo.	13 mo.	12 or 14 mo.
Vegetables, when started	18 mo.	2 yr.	11 or 12 mo.	Under 1 yr.	2 yr.	12 or 14 mo.
Orange juice	0	±	+	++	0	+
Cod liver oil	0	0	0	0	18 mo. to 2 yr.	0
First teeth: Time of eruption	10 mo.	4 mo.	6 mo.	?	Very late	5 mo.
Condition	Good	Good	Good till ill at 5 yr.	Good till 5 yr.	Poor	Poor
Care	0	0	0	Boric	0	0
After First Year						
Diet: Milk	++++	++	+++	++++	±	++
Meat	0	+	+	++	+++	+
Eggs	++	+	++	+	++	++
Green vegetables	+	+++	+++	++	+	++
Fruits	++	+	+	+	+	+++
Cereals	++	++	+	+	++	++
Potatoes	+++	+++	++	+++	++	++
Sweets	++	+	++	++	+	++
Candy	+++	++	++	+++	+	++
Teeth: Brushing	+	±	++	++	++	++
Dental care	0	0	0	Some	0	2 extractions
Diseases: Rickets	0	0	0	0	+	0
Scurvy	0	0	0	0	0	0
Convulsions	0	0	0	0	0	0
Measles at	7 yr.	8 yr.	5 yr.	7 yr.	7 yr.	4 yr.
Mumps at	1 yr.	0	5 yr.	0	0	5 yr.
Pertussis at	1 yr.	9 yr.	5 yr.	0	0	¼ yr.
Chickenpox at	8 yr.	9 yr.	5 yr.	⅛ yr.	0	6 yr.
Scarlet fever at	0	3 yr.	4 yr.*	0	7 yr.	0
Diphtheria	0	0	0	0	0	0
Respiratory	Frequent colds	Many colds; pneumonia at 15 months	Pneumonia at 2 yr. teeth "spotted" after it	±	Many colds and croup	+
Other diseases	Otitis media, under 1 yr.	Very sick at 6 weeks	..	0	0	0
Outdoor play	+	++	+++	++	+++	++
Comment	..	Does not chew food				

* Teeth loose after scarlet fever.

PRENATAL PERIOD

The health of the mothers of sixteen children in the first group and of eighteen of the second group was good. This difference is, of course, too small to be of any significance.

TABLE 3.—*Summary of Fifty Cases*

	Group 1 Good Teeth	Group 2 Poor Teeth
Average age	9.5 years	6.1 years
Prenatal Period	Cases	Cases
Good general health	16	18
Green vegetables, fruit, milk predominating in diet	14	10
Carbohydrates predominating	6	10
Outdoor exercise (++ or +++)	9	6
Dental trouble (++ or +++)	6	6
Heredity		
Poor (+++), or very poor (++++) in both parents	2	11
Good (+), or very good (0) in both parents	7	..
Total number of parents with very poor teeth	2	13
Total number of parents with very good teeth	9	2
First Year of Life		
Good general health	22	19
Premature birth	..	4
Breast-fed more than nine months	11	11
Breast-fed less than one month	4	4
Cereal before nine months	11	16
Vegetables before one year	14	14
Vegetables before nine months	4	2
Orange juice (+++ or ++++)	3	5
Cod liver oil	1	1
First tooth erupted before seven months	13	8
After First Year of Age		
Green vegetables, fruit, meat, eggs, predominating in diet	13	3
Carbohydrates predominating	3	14
Candy and sweets (++ or more each)	2	14
Milk (+++ or ++++)	6	12
Cod liver oil	1	4
Brushing of teeth (++ or +++)	9	15
Outdoor play (+++ or ++++)	12	13
Diseases		
Rickets	4	6
Scurvy	0	1 ?
Measles	22	25
Mumps	11	6
Pertussis	16	17
Chickenpox	15	17
Scarlet fever	..	7
Diphtheria	..	..
Frequent colds or croup	1	10
Frequent tonsillitis	2	..
Otitis media	1	3
Pneumonia	1	3
Other diseases	9	9
Total	82	104
Average number of diseases for each child	3.28	4.16
Children with less than four illnesses	14	8
Children with more than four illnesses	3	10

Nine mothers of the first group and six of the second had more than the average amount of outdoor exercise during pregnancy. Here again the difference is too small to be of significance, and also the percentage of the group, less than half in each case, is too small to be

significant. Six mothers in each group had had a great deal of dental trouble during pregnancy.

A greater difference existed in the two groups with regard to the mother's diet during pregnancy. Green vegetables, fruits and milk were found to predominate in the diet of fourteen of the mothers of the first group and of ten of the second group, whereas meat, potatoes and sweets was the predominating diet of six of the first group and of ten of the second. The predominance of one type of food over the other is designated by plus signs (tables 1 and 2). Thus, + signifies from one to two average sized servings of the food each day; ++ from two to three servings; +++ from three to four servings; ++++ four or more servings, and ± food not served daily but usually two or three times a week. Thus, ±± were considered as equal to + (case 1). For example, meat ±, potato + and sweets ± = ++. Vegetables ++, fruits ++ and milk 0 = ++++. A difference of + or more between the totals is considered as a predominance of that type of food. It was difficult to obtain accurate information on this point. In only a few cases had the mother paid any special attention to her diet. In most cases it was only possible to learn of what her present diet consisted, whether it had differed during pregnancy and if so, in what respect. The difference in this respect between the two groups was slightly greater than with reference to other factors. The data in the two groups make it reasonable to conclude that an abundance of fruit, vegetables and milk in the mother's diet during pregnancy is of some important significance in the production of healthy teeth in the child.

None of the children with good teeth was prematurely born, but four of those with poor teeth were prematurely born. The significance of this point is doubtful.

INFANCY

Eleven children in each group were breast-fed for more than nine months, and four in each group were breast-fed for less than one month. Breast feeding, therefore, would seem to be an unimportant factor.

Cow's milk was used almost entirely for complementary or supplementary feedings. Preparations such as malted milk, Mellin's food, Dryco and Eagle brand were used for a few weeks in several cases, but in only one case (case 47, poor teeth) was its use (malted milk in this case) continued for most of the nursing period.

Cereal feedings were started before the age of 9 months in eleven of the first group and in sixteen of the second, suggesting that carbohydrate foods are factors in the decay of teeth.

Vegetables were regularly given before the age of 1 year to fourteen of each group, and before the age of 9 months to four of the first group and to two of the second group.

Orange juice was given regularly to three children from 5 to 6 months of age of the first group and to five of the second. The number is too small to be significant.

Only one child in each group was given cod liver oil during the first year of life. Five others, one with good teeth and four with poor teeth, were given the oil after the age of 1 year either because of definite rickets or for some other debilitating condition.

Thirteen children of the first group and eight of the second group cut their first teeth before 7 months. This seems to contradict the popular belief that an infant who cuts teeth late has better teeth than one who cuts them early.

AFTER ONE YEAR OF AGE

The greatest difference between the two groups occurred in connection with the diet of the children after the age of 1 year. Green vegetables, fruit, meat and eggs predominated in the diet of thirteen of the children with good teeth, and in only three of those with poor teeth, whereas carbohydrates predominated in fourteen of those with poor teeth, and in only three of those with good teeth. Similarly, fourteen of those with poor teeth, and only two of those with good teeth ate a great deal of candy and sweets.

It was possible to obtain much more detailed information regarding the diet of the child than that of the mother during pregnancy. Eight kinds of food were considered: cereals, potatoes, sweets (cakes, puddings, pies) and candy being the carbohydrate foods, and meat, eggs, vegetables other than potatoes and fruit constituting the so-called meat and vegetable type. One kind of food, carbohydrate, for example, was said to predominate only when plus signs for those foods exceeded the plus signs for the meat and vegetable foods by two (++) or more. The difference between the groups in this instance is sufficient to leave little doubt that it is significant in dental decay.

Milk was considered separately, and it was found that six children of the first group drank three or more glasses a day, while twelve of the second group drank that amount. Carbohydrates predominated in the diet of three of the six in the first group, and vegetables in two; one ate approximately equal amounts of each. Carbohydrates predominated in the diet of nine of the twelve children who drank milk in the second group and vegetables in the diet of one; two ate equal amounts of each. This suggests that milk, when served in fairly large quantity, is more likely to crowd out vegetables and fruit than carbohydrates, and yet that the milk is not as effective as the fruits and vegetables in preventing dental decay.

The mothers of ten children, four of the first group and six of the second, cleansed the teeth daily during the first three or four years. Regular brushing of the teeth one or more times daily (recorded as care

of the teeth + + or + + + +) was carried out by nine of the group with good teeth, and fifteen of those with poor teeth. Brushing, therefore, appears to be useless in preventing decay.

The amount of outdoor play was approximately the same in both groups.

DISEASES

The general health of twenty-two of the children with good teeth and of nineteen with poor teeth was considered good.

In considering the question of diseases the most marked difference is found in the total number of diseases in each group: 82 in the first group and 104 in the second. This difference becomes more striking when it is noted that the average age in the first group was 3.4 years greater than that in the second. In considering the diseases individually, little difference was noted except in three instances. A history of frequent colds or croup was given of ten of the twenty-five children with poor teeth, and of only one with good teeth. Seven children with poor teeth had had scarlet fever; none with good teeth had had it. Eleven of those with good teeth and only six of those with poor teeth had had mumps. Caries was thought to have followed immediately after acute illnesses of five children (scarlet fever in two, cases 30 and 48; chorea in one, case 47; pneumonia in one, case 30, and severe illness at the age of 9 months diagnosed merely as tonsillitis in one, case 40).

The average number of illnesses of each child in both groups was 3.7; in the first group, 3.28, and in the second, 4.16.

These data indicate that disease, or infection (for practically all the diseases that were mentioned were infectious in nature), is also significant in the decay of teeth.

HEREDITY

The consideration of an herditary factor raises many questions. The data suggest that it is important, for in the first group only two parents of fifty had very poor teeth (caries + + + +), while in the second group there were thirteen. In the first group nine parents had very good teeth, and in the second only two. In the first group there were two children whose parents had poor teeth (caries + + + or + + + +), while in the second group there were eleven. In the first group, both the father and mother of seven children had good teeth (caries 0 or +); in the second group, there was no case in which both parents had good teeth. From these data it would appear that heredity is significant etiologically; however, good teeth in all members of the same family may be due to correct diet, healthy environment and good care. On the other hand, of the seven children in the first group whose parents had good teeth, three (cases 7, 22 and 23) had diets predominating in green

vegetables and fruits, and had not had any diseases except measles, mumps and whooping cough; two of the seven (cases 18 and 21) had diets in which the two types of foods were about equal. One child (case 21) was fond of coarse foods; the mother's diet during pregnancy had contained an abundance of green vegetables and fruit, and the only diseases that the child had had were measles, mumps and chicken pox. One child (case 18) had had only measles and croup. One child (case 19) had had a diet in which carbohydrates predominated; the mother's diet during pregnancy had been equally proportioned. The child had had measles and chicken pox. One child (case 16) had been on a diet of carbohydrates; the mother's diet during pregnancy had been equally proportioned; the child had had rickets, measles, chicken pox and frequent attacks of tonsillitis with earache until tonsillectomy was performed at the age of 5.

Thus in six of seven cases there seems to be adequate explanation for the good teeth on the basis of correct diet, or comparative freedom from infection, or both, without considering heredity. In the last case such an explanation cannot be found, and it may be that in this one the hereditary factor has been responsible for the resistance of the teeth to the harmful effects of a carbohydrate diet, and repeated infections.

In thirteen cases, both parents had poor teeth. Two children in this group (cases 4 and 5) had good teeth, and the teeth of the remaining eleven were poor.

In cases 4 and 5, fruit and green vegetables had predominated in the diet of the mother during pregnancy and also in the child's diet; neither child had had scarlet fever or frequent colds, but both had had measles, mumps and chicken pox; one had also had whooping cough, and the other a mild attack of anterior poliomyelitis. The mother of one child (case 5) said she had made a definite attempt to guard her boy's teeth through her own diet during pregnancy, and the child's diet, because her own teeth had been so poor. Her success would indicate that if a tendency to dental caries is inherited it can be overcome by careful attention to diet and the prevention of infection.

Five of the group of eleven children (cases 29, 37, 38, 42 and 48) had had frequent colds; four (cases 29, 48, 49 and 50) had had scarlet fever; six (cases 29, 40, 47, 48, 49 and 50) had had a predominantly carbohydrate diet; one (case 47) had had chorea at the age of 6, after which his teeth rapidly became much worse; one (case 40) had had a severe illness at the age of 9 months immediately after which his teeth began to decay. All but two (cases 43 and 45) of the eleven children manifested at least one, and in most cases three or four, of the other features which seem to be of significance in dental decay.

SUMMARY

The difference in the data obtained in the two groups is not so striking as one would expect. The only feature that seems to be of definite etiologic significance in preventing decay of teeth is a diet composed largely of fruits and vegetables. Heredity, infectious diseases and care of the teeth appear to be of little, if any, significance.

A POSSIBLE CAUSAL FACTOR OF FOOD ALLERGY IN CERTAIN INFANTS*

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During the first years of my work on allergy, I chanced on a statement in an article by Wells [1] that offspring born of guinea-pigs fed on oats were moderately sensitive at birth apparently from a passive sensitization conferred by the mother.

The question arose in my mind whether in the human being there could be any relationship between a mother's diet during pregnancy and her child's hypersensitiveness to certain foods.

At this time, a child (case 1), aged 13 months, suffering from a severe eczema involving the head, face, extremities and trunk was brought to me at the New York Nursery and Child's Hospital. Allergic skin tests revealed a positive reaction to egg white. I promptly proceeded to inquire carefully into the antepartum diet of the mother of this child and found that one of the few foods she could tolerate during gestation was egg, and that she ate from seven to eight eggs a day, mostly in the form of egg-nogs.

At about the same time, another case was referred to me privately that of a boy (case 6), aged 5 years, who had been suffering from asthma for a year. Positive skin reactions were obtained to various nuts. The antepartum history revealed the fact that the mother had had a craving for nuts and had eaten a pound a day.

From this time (1921), I systematically took most careful antepartum histories in my cases in which protein sensitiveness occurred, and the evidence I found made me consider that overindulgence in particular foods during gestation might be a causal factor in the subsequent food allergy of certain children.

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1. Wells, H. Gideon: Studies on the Chemistry of Anaphylaxis: III. Experiments with Isolated Proteins Especially Those of the Hen's Egg, J. Infect. Dis. **9**:147, 1911.

I have chosen the following cases [2] to demonstrate the various types of allergic manifestations occurring in this group.

REPORT OF CASES

CASE 1.—F. I., aged 17 months, was breast fed for six months. At 3 months of age, a mild eruption first appeared. At 7½ months, egg was given for the first time and added to the formula each day; no history of vomiting was obtained, but eczema began to develop. It became progressively worse until the child was brought to me at the New York Nursery and Child's Hospital at 14 months of age, with an eczema of the most severe type, which involved the entire face, neck and scalp (hair destroyed) and both legs and arms; the body was moderately involved.

The antepartum history showed that the mother took seven to eight eggs a day throughout the antepartum period, mostly in the form of egg-nogs. She had an aversion for other foods, but tolerated eggs. The postpartum history showed that she took three eggs a day for one month after the child's birth; then normal diet was resumed. The protein skin tests resulted in positive reactions to egg white and egg yolk.

With ordinary local treatment and absolute elimination of egg-containing foods, the condition rapidly improved. It is interesting to note in this history that the child, within a period of three months of observation, developed a definite asthmatic attack which followed an inadvertent taking of egg-containing food.

CASE 2.—D. G., aged 6 months, was first seen by me at 8 weeks of age, with an eczema of both cheeks and seborrhea of the scalp. The child had been given a simple milk formula supplementing the breast milk, seven weeks before coming to me. When this formula was given, the child vomited and then developed eczema. The antepartum history revealed that the mother took from 2 to 3 quarts of milk and from three to four eggs a day. According to the postpartum history, she did not eat excessively of any kind of foods. The protein skin tests showed a positive reaction to lactalbumin and whole milk.

The child was given a denaturized milk formula instead of the whole milk, which she tolerated without vomiting. She was observed for four months; at the end of that time there was a complete cessation of the eczema.

CASE 3.—L. G., aged 16 months, when first seen by me at 14 months of age, was suffering from a marked, chronic, thick, itchy eczema, which was present over the face, trunk and extremities. When the child was 1 month old, while fed on breast milk, seborrhea was present, but not eczema. When 3 months old, the baby developed a mild eczema coincident with the taking of orange juice and with weaning. At 5 months of age, it is interesting to note that the eczema cleared up entirely. This was during the summer months, and the mother, afraid that the child might have summer complaint, discontinued the orange juice and all egg-containing foods, for the baby had been given eggs and crackers before this period. At 7 months, the child was given soft boiled egg, which he promptly vomited. Several attempts to give him egg after that, failed. From that time

2. In all these cases, only the salient features of the particular child's allergic state is given. When excessiveness or cravings for particular foods are given in the antepartum and postpartum history, this means that these particular foods are taken in excess of the regular diet. The protein skin tests made on the children were also performed on the mothers, and in all of the mothers, the skin reactions were negative.

on, the eczema persisted, at times showing marked exacerbation, and at other times marked improvement. The antepartum history disclosed that the mother took egg-nogs every day containing raw eggs. The postpartum history showed that she continued these egg-nogs during the nursing period, averaging from one to three eggs a day, generally three eggs. The protein skin tests showed a positive reaction to egg white. It was advised that the child should not be given eggs in any form. Desensitization was commenced subcutaneously with egg white. After a period of two months, the eczema was definitely improved.

Case 4.—B. T., was first seen by me when he was 6 months of age; he was suffering from mild roughness of both cheeks. The child was entirely breast fed. I inquired into the antepartum history and found that the mother had had from three to four eggs a day; postpartum, the same number were ingested. The protein skin tests gave positive reactions to egg white.

Nothing further is known about this case, the child never having received eggs in any form. This mild roughness of the cheeks may have been caused by the mother's indulgence in eggs during the antepartum and postpartum periods. The positive skin reaction showed clearly how a diagnosis can be made in the case of a patient who is potentially sensitive even before he ingests the particular food to which he is sensitive.

Case 5.—R. K., aged 1 year, when first seen by me had a crusted, dry, bleeding area on both cheeks and on the forehead; it was also spreading to the back and chest. The child had been weaned at 6 months, and had been given an ordinary milk formula, which he took well. When the child was between 7 and 8 months of age, the mother gave him soft boiled egg. With the first teaspoonful the child began to cry; he then got red and hives developed all over the body. The child did not vomit. This urticarial reaction lasted for about two hours. Egg was not given after this, but the mother fed the child zweiback and egg-containing food, such as sponge cake. A slight eczema began to develop. At 11 months she began giving the child soft boiled egg again. This time the child vomited the egg promptly. The mother again discontinued egg and began to give charlotte russe and egg-containing foods, and the eczema became progressively worse. The antepartum history showed that the mother took two egg-nogs every day and ate a great deal of cake and pastry. The postpartum history disclosed that she took four eggs a day, but not much pastry. The protein skin tests revealed a positive reaction to egg white.

The mother was advised not to give the child eggs. Local treatment was given and the child disappeared from observation.

Case 6.—E. H., aged 5, was referred to me with a history of having had asthma for the past year. The child's attacks seemed to be related to intake of foods, as they occurred after certain meals. There had been no allergic manifestations up to the fourth year. A striking antepartum history was disclosed in that the mother had indulged excessively in nuts throughout her period of pregnancy, as she claimed to have eaten about a pound a day. The protein skin tests showed a positive reaction to Brazil nuts, pecans, hickory nuts and walnuts.

This is a type of sensitivity which was probably transmitted through the mother, and which was not manifested until the patient was 4 years of age, at which time he started to eat nuts. The physician who referred the case to me believed the attacks were caused by candies and cakes. When I obtained the antepartum history, the first tests that I tried on the child were to discover his reaction to nuts, as such tests were so strikingly indicated in the history. The child was observed for many months; his condition was reported as favorable when he did not eat nuts.

CASE 7.—A. R., aged 7, had been coming regularly to me as a normal feeding case, and was entirely free from allergic manifestations up to 9 months of age. Up to this time, the child had not had egg in any form. The mother gave her hard boiled egg (boiled for thirty minutes) in small amounts without any untoward results. At 10 months of age, when the child was receiving a whole hard boiled egg, the mother was advised to start giving coddled egg, and with the first small offering of this form of egg, a severe attack of vomiting resulted, which shortly followed by an intense urticarial reaction, involving the entire body. The antepartum history showed that the mother ate inordinately of egg-containing foods, particularly custards and pastries. The postpartum history showed that for the first two week period in one of the large hospitals in New York, the mother received an egg-nog each day, besides custards, eggs and egg-containing foods. The protein skin tests resulted in positive reaction to egg white several days after the urticarial reaction and a number of times throughout the subsequent year.

For a period of two years, the child was treated for her intolerance to eggs. For one whole year, egg in every form was kept out of her diet. Following this, minute doses of raw egg white were given each day, and after a period of six months of this treatment, the feeding of hard boiled egg was resumed, and then gradually egg-containing foods were given in small amounts. After a period of about a little more than two years the skin reaction disappeared, and the child was again cautiously given egg-containing foods. It is now seven years since the child was first brought to me, and she has been partaking of eggs and egg-containing foods, and has never had an allergic reaction in any form since the explosive first attack. This indicates what excellent preventive measures can be instituted in cases in which allergic manifestations of this nature are diagnosed at their inception.

CASE 8.—R. K., aged 18 months, was first seen by me at 4 months of age, suffering from a marked eczema of the intense, bleeding, itchy type. The child did not show any allergic manifestation while he was breast fed for the first two months of life, after which he was placed on a milk formula and orange juice; he then developed eczema. The antepartum history showed that the mother took about 1 quart of milk and six oranges a day. According to the postpartum history, there was no overindulgence in any particular foods. The protein skin tests showed a positive reaction to lactalbumin and beef serum, and a suggestive reaction to oranges.

The child was observed by me for a period of eighteen months, and has done remarkably well on denaturized milk formula and tomato juice which was substituted for orange juice. As the mother lived at a considerable distance from New York, certain interesting information was gleaned through correspondence. Five months after the child had been under treatment and the eczema was entirely cleared the mother was instructed to give beef juice, starting with a few drops, and also to introduce 1 ounce of raw milk to the entire day's formula. This was continued for about five days, and when the beef juice was increased up to 1 teaspoonful and the raw milk to 6 ounces (added to the entire amount of the denaturized formula) two and one-half hours after ingestion of the beef juice, the child's face became red, urticaria developed on the forehead and around the eyes. Within a few hours he also developed severe diarrhea, having green undigested mucus-containing stools every half hour. This continued throughout the night. The beef juice and the raw milk were then discontinued, and after about one week, the diarrhea cleared up. Several months later, beef juice was again tried with the results already noted. Since then, the child has been fed

entirely on the denaturized milk formula and kept away from all forms of beef, and he has thrived normally. He is still under observation.

CASE 9.—F. W., aged 13 months, was 1 year of age when first seen. The mother gave a history of a colicky baby having attacks of itchy eruptions and hives and frequent attacks of vomiting. The child was entirely breast fed for six months, and did not have any allergic manifestations. At 7 months of age, the whole milk formula was begun, supplementing the breast feeding. It was difficult to give the child the formula, because he refused it, but when forced to take it, he vomited. Green stools with mucus were noted. The child never took the milk well. At 9 months of age, egg was fed, which was promptly vomited. Throughout this period, up to the age of 10 months, there was poor gain in weight. At 10 months, the child was weaned and placed on the milk formula. When the entire bottle was forced at this time, there was a severe attack of vomiting, which continued throughout the night. He then developed hives, which cleared up the following morning. The baby was not given milk for one week and was fed zweiback and water. This was continued with the addition of broth, crackers and cereals for two months more. The feeding of milk was not resumed up to the time I saw the child when he was 1 year of age. A week before admission to the hospital the feeding of egg was tried again, and was followed by a severe attack of vomiting. The antepartum history showed that the mother took two eggs for breakfast, one egg-nog and 1 quart of milk a day, and ate a great deal of icecream and cakes. According to the postpartum history, she continued to ingest 1 quart of milk a day, one egg-nog, icecream and a great deal of cake. The protein skin tests were positive to cow's milk, beef serum and egg white.

The child was observed for a short period. He was placed on the denaturized milk formula, which was well tolerated. Egg was entirely eliminated from the diet.

CASE 10.—W. S., aged 1 year, when first seen was suffering from asthma and moderate eczema. The feeding of egg was started two months before admission into the clinic—soft boiled egg. The child vomited this, but allergic manifestations were not evidenced. The feeding of egg, however, was continued, and a few days before the child was seen, he developed a typical attack of asthma which lasted for about three days. Signs in the lungs were still present when he was examined by me. At about this time he also developed moderate eczema of both cheeks. The child was given egg each day; he returned to the clinic five days later with asthmatic breathing still present, and the eczema was spreading on the forehead. The antepartum history showed that the mother took three to four egg-nogs and 2 quarts of milk a day, eggs beside those in the egg-nogs, and a great deal of pastry. The postpartum history showed that the mother took two egg-nogs a day, and one glass of malted milk containing a raw egg, besides 1 quart of milk a day. There were no allergic manifestations during the nursing period. The protein skin tests were performed, but repeated attempts to elicit skin reactions failed, the child at no time giving a positive reaction to egg.

Eggs were eliminated from the diet, and the following week the lungs were clear. The mother was then advised to perform a clinical test. The child was given a raw egg each day in the formula, and was given egg besides. The mother reported sixteen days later that each time she gave egg, he refused it, and when it was forced, to the extent of only 1 teaspoonful, he vomited the entire contents of his stomach. Each time following the administration of egg, the child's face became red. The asthmatic breathing returned five days after this clinical experiment had been started. The mother, however, continued giving egg as I had

advised, and eleven days later, that is, when the child returned to the clinic, the eczema was present on both cheeks, but somewhat more marked than before. The lungs, however, were clear, indicating that the child was going through a refractory period. This clinical experiment, to my mind, is as definite as the skin reaction, and therefore eggs were discontinued in every form, and the child was observed for another two months. The eczema definitely improved, and throughout this two months' period, there was no recurrence of asthmatic breathing. The child disappeared from observation.

Case 11.—P. Mc., aged 20 months, was first seen at 10 months of age, with dry, itchy eczema on the face and on both extremities. The baby was breast fed for six months, after which time he was put on an irrational diet, particularly rich in bananas. At 9 months of age, the infant developed eczema. The antepartum history showed that the mother ate four bananas a day throughout her antepartum history. According to the postpartum history, she ate four bananas a day also after the child's birth. Protein skin tests were made over a period of ten months with banana protein. After the child had been tested month after month, she gave a suggestive reaction at the fourth month of observation and at the tenth month of testing, there was a definite reaction to bananas.

Throughout this period of ten months of observation bananas were eliminated from the diet. Local treatment was applied to the eczema, and there was no recurrence of the skin condition.

Case 12.—J. M., aged 8 months, had marked crusted, bleeding, itchy eczema on both forearms, face, forehead and seborrhea of the scalp. The child was breast fed for four months. At this time, the mother developed an abscess of the breast and started to wean the child by feeding it on whole milk formula. The child took the formula well. The only other foods that had been given were cakes and zweiback, the feeding of which had been started shortly after the formula. The child did not have eczema or seborrhea for the first four months. One month after the feeding of the formula and cake had been started, mild eczema developed on the cheeks and gradually became worse. In the week before admission, the eczema became markedly aggravated. The antepartum history showed that the mother took 2 quarts of milk and two raw eggs a day and ate a great deal of pastry. According to the postpartum history, she ingested 1½ quarts of milk and two raw eggs a day and pastry. It is interesting to note here that the mother had had hives when she was a child. Another child, 3 years of age, did not have any allergic manifestations, and the mother definitely stated that she did not indulge excessively in eggs or milk before this child was born. The protein skin tests resulted in positive reactions to egg white, and negative reactions to cow's milk.

The child was observed for about one month. There was moderate improvement of the eczema, and then the child disappeared from observation.

Case 13.—E. R., aged 10 months, was first seen at 8 months of age, presenting a marked, bleeding eczema, of five months' duration, involving both cheeks. The child had been breast fed for three months, and had then been placed on cow's milk formula. Shortly after this, eczema developed. The history is indefinite as to diet from then on, because the child was carelessly fed. The antepartum history showed that the mother consumed from six to seven eggs a day, which included egg-nogs, and 3 quarts of milk. The postpartum history was negative, except that for the first two weeks the mother ingested from two to three egg-nogs and 1 quart of milk a day. The protein skin tests showed a positive reaction to egg yolk and egg white at several examinations and a negative reaction to milk protein.

This case was observed for two months. The child was placed on a denaturized formula, and all forms of egg-containing foods were kept out of the diet. The eczema improved considerably.

CASE 14.—G. K., aged 7½ months, was first seen at 7 months of age, when she was suffering from urticaria which had persisted for the past three months. For the first three or four months of life the child had so-called colic; she vomited and had loose green stools, yet gained well. When the child was 1 month of age, she developed hives; new lesions appeared practically every day. They were small and shotty. At times, they would be large, and would disappear rapidly, but when small, they would remain for several days and were extremely itchy. The child was still breast fed and had received supplementary feeding since about the fourth month. The mother found great difficulty in giving supplementary feeding, which had to be forced. When the child finally took the formula, she usually vomited, the milk coming up before it had curdled. Before the child vomited, she became cranky; she felt much relieved when the contents of the stomach were emptied. When the child was seen by me at 7 months of age there was definite evidence of a typical urticarial eruption. The antepartum history showed that the mother drank 2 quarts of milk a day; the postpartum history that she took 2 quarts of milk a day for the first two months and then four quarts up to the present time. The protein skin tests were positive to lactalbumin of cow's milk.

The mother was advised to decrease the milk intake considerably. The child was placed on denaturized formula, and all the milk that the mother took was also to be denaturized. The child was observed by me for a period of about one month on this denaturized milk regimen, and during this time the urticaria did not recur.

CASE 15.—M. G., aged 7½ months, was admitted to the allergy clinic of the Sydenham Hospital with a history of having suffered from eczema of both cheeks. The eczema was extremely itchy and dry. The antepartum history showed that the mother had indulged almost continuously in wheat-containing foods, ate a loaf of bread a day, two large pies a week, cakes and crackers all the time throughout her antepartum period. According to the postpartum history, she discontinued the excessive consumption of wheat. The protein skin tests were positive to all the wheat proteins.

While giving the history, this mother said that up to 6 months of age, when the child was breast fed, there was no evidence of eczema, but for the past month and a half, since the baby had been given wheatena and cream of wheat, eczema had begun to develop. When I obtained the striking antepartum history, I asked my assistant to make protein skin tests for wheat on the child, with the resulting strong reactions obtained to the wheat proteins. Just such a situation has been obtained in most of the foregoing cases.

Many more cases that I have records of could be cited, but the foregoing group, I believe, is typical and exemplifies the various types of allergic manifestations encountered.

COMMENT

I withheld publication of these clinical records, however, for seven years, feeling that such evidence was insufficient, and the meager amount of experimental proof that I was able to find at the time did not justify the voicing of the foregoing theory.

Since then, I have had an opportunity [3] to investigate the problem systematically under controlled conditions in the guinea-pig.[4]

The first problem undertaken in this experimental work was an exhaustive study of the rôle of the placenta [5] in the transfer of heterologous substances. In a previous study,[6] it was demonstrated that the animal kingdom may be divided into several groups according to certain histologic differences in the placentas. One group, in which the ruminants were included, has placentas that consist of several cell layers separating the fetal from the maternal circulation, and are generally impermeable to the passage of substances. Another group to which the human being and guinea-pigs belong has only a single cell layer separating the fetal from the maternal circulations, and in these the placenta is extremely permeable to the passage of many forms of heterologous substances.

In the present study,[5] the earlier work was corroborated and it was proved that the placenta in guinea-pigs and human beings is a permeable membrane and permits the transfer of heterologous substances. This gives a basis for the assumption that antigens can be transferred from the maternal to the fetal circulation and thus permit sensitizing substances to enter the fetus.

The rôle of colostrum [7] was next considered, and, except in the case of ruminants and mice, it was found that colostrum played a negligible rôle in the passage of substances from the mother to the offspring.

The third step was to study the rôle that milk [8] had in the possible transfer of proteins. I was confronted with a dramatic demonstration made several years ago by Shannon,[9] wherein he attempted to show that proteins may pass through the breast milk and thus be the cause of food

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3. Crane Research Fund for the Study of Allergy in Children.

4. Ratner, B.; Jackson, H. C., and Gruehl, H. L.: Active and Passive Protein Sensitization in Utero, Proc. Soc. Exper. Biol. & Med. **23**: 327, 1926; Transmission of Protein Hypersensitiveness from Mother to Offspring; Study 1. Critique of Placental Permeability, J. Immunol. **14**:249, 1927; Study 2. The Rôle of Colostrum, ibid., p. 267; Study 3. The Rôle of Milk, ibid., p. 275; Study 4. Passive Sensitization in Utero, ibid., p. 291; Study 5. Active Sensitization in Utero, ibid., p. 303.

5. Ratner, Jackson and Gruehl (footnote 4, second reference).

6. Kuttner, A., and Ratner, B.: The Importance of Colostrum to the New-Born Infant, Am. J. Dis. Child. **25**:413 (June) 1923.

7. Ratner, Jackson and Gruehl (footnote 4, third reference).

8. Ratner, Jackson and Gruehl (footnote 4, fourth reference).

9. Shannon, W. R.: Demonstration of Food Proteins in Human Breast Milk by Anaphylactic Experiments on Guinea-Pigs, Am. J. Dis. Child. **22**: 223 (Sept.) 1921; Anaphylaxis to Food Proteins in Breast Fed Infants and Its Probable Relation to Certain Disturbances of the Nursing Infant, Especially Exudative Diathesis, Minneapolis Med. **5**:137, 1922.

allergy in the young infant. His work, however, is open to criticism from the experimental standpoint, and Stuart,[10] working with Schloss, has shown that his results are not valid. The experiments, as well, did not demonstrate this transfer in the guinea-pig.

In our next study,[11] it was shown that a sensitized mother animal can transfer antibodies to her offspring, which confirmed the earlier work of Rosenau and Anderson.[12]

A large number of families were studied wherein the guinea-pig mothers were sensitized to horse serum before gestation, and in all cases the guinea-pigs were born sensitive to horse serum, and on first contact with horse serum intravenously, they demonstrated unmistakable signs of acute anaphylactic death or severe anaphylaxis. It was further shown that this sensitiveness persisted throughout the life of the mother, who passively transferred this sensitive state through litter after litter; it was also shown that passive hypersensitiveness of the offspring could persist for a period of three months, after which it wore off, thus demonstrating anew its strictly passive nature. Because of its transitory character, it could not be transferred to the second generation.

It was then that we undertook the problem of greatest interest for which there was no experimental evidence thus far, namely, to demonstrate that a mother who was not sensitive to a substance at the time of parturition could give birth to an offspring that had been sensitized in utero.

This was a difficult task to prove, but in the last study,[13] evidence was presented which showed the possibility of actively sensitizing a fetus. The general impression is that new-born animals cannot be actively immunized, so that in order to show that this same situation does not obtain with sensitization, it was shown in this study that new-born guinea-pigs could be sensitized in the ordinary manner, providing a suitable incubation period elapsed between the sensitizing and the intoxicating injections.

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10. Stuart, H. C.: The Excretion of Foreign Proteins in Human Milk, Am. J. Dis. Child. **25**:135 (Feb.) 1923.

11. Ratner, Jackson and Gruehl (footnote 4, fifth reference).

12. Rosenau, M. J., and Anderson, J. F.: A Study of the Cause of Sudden Death Following the Injection of Horse Serum: Hereditary Transmission of the Susceptibility in Guinea-Pigs, Bull. Hyg. Lab. U. S. P. H. S. **29**:73, 1906. Anderson, J. F.: 1. Maternal Transmission of Immunity to Diphtheria Toxin. 2. Maternal Transmission of Immunity to Diphtheria Toxin and Hypersusceptibility to Horse Serum in the Same Animal, Bull. Hyg. Lab. U. S. P. H. S. **30**:7, 1906; Simultaneous Transmission of Resistance to Diphtheria Toxin and Hypersusceptibility to Horse Serum by the Female Guinea Pig to Her Young. J. M. Research **10**:259, 1906.

13. Ratner, Jackson and Gruehl (footnote 4, sixth reference).

This proved, nonsensitive mothers were injected with horse serum a few days before parturition. The litters were shown to be nonsensitive at the time of birth, as one of the offspring of each litter, injected with horse serum shortly after birth failed to demonstrate any anaphylactic symptoms; this was in striking contrast to the former study in which it was found that the offspring of sensitive mothers were sensitive at birth. The mothers were also shown to be nonsensitive at the time of parturition. The remaining offspring of each litter after a period of about a month were given an initial intravenous injection of horse serum which produced anaphylactic death or unmistakable anaphylactic symptoms; this indicated that these guinea-pigs actually received their initial sensitizing dose while in the uterus and developed an active state of hypersensitiveness within a month after birth, thus proving the hypothesis that active sensitization in utero can occur.

In view of the fact that the human being and the guinea-pig both belong to the same placental group, I feel justified in applying these experimental results to the human being, and can therefore assume that a human fetus can in like manner become actively sensitized in the uterus.

It is of fundamental importance at this point to state that anaphylactic or allergic sensitization cannot take place unless the sensitizing substance is a protein and not a product of protein cleavage such as a polypeptid or amino-acid. Physiologists in general believe that proteins are broken down into amino-acids before they can enter the circulation, but there is evidence that proteins may enter the circulation without being broken down.

Ascoli [14] has shown that proteins pass through the placenta. Van Alstyne [15] has shown that proteins pass through the intestinal wall of the dog. Schloss and his co-workers [16] have shown that proteins may pass through the intestinal tract and enter the circulation directly. Freeman [17]

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14. Ascoli, A.: Passiert Eiweiss die placentare Scheidewand? Ztschr. f. phys. Chem. **36**:498, 1902.

15. Van Alstyne, E. V. N.: The Absorption of Protein Without Digestion. Arch. Int. Med. **12**:372 (Oct.) 1913.

16. Schloss, O. M., and Worthen, T. W.: The Permeability of the Gastroenteric Tract of Infants to Undigested Protein, Am. J. Dis. Child. **11**:342 (May) 1916. Schloss, O. M., and Anderson, A. F.: Allergy to Cow's Milk in Infants with Severe Malnutrition, Proc. Soc. Exper. Biol. & Med. **20**:5, 1922. Anderson, A. F., and Schloss, O. M.: Allergy to Cow's Milk in Infants with Nutritional Disorders, Am. J. Dis. Child. **26**:451 (Nov.) 1923. Anderson, A. F.; Schloss, O. M., and Myers, C.: The Intestinal Absorption of Antigenic Protein by Normal Infants, Proc. Soc. Exper. Biol. & Med. **23**:180, 1925.

17. Freeman, J.: Paroxysmal Rhinorrhoea, J. Laryng. & Otol. **40**:561, 1925.

and Walzer [18] have demonstrated the presence of protein in unchanged form in the blood of adults.

In the work of Schloss, and Freeman and Walzer, the indications are that even in the case of the ingestion of normal amounts of protein, undigested protein can be demonstrated in the blood. Hence, in the cases in which I have shown that unusual amounts of protein were consumed by the pregnant mother, there is even greater likelihood that undigested proteins were present in the maternal circulation.

Therefore, while in the guinea-pigs the proteins were injected parenterally, in the human mother, the proteins must have gained entrance into her circulation through the digestive tract, and were thence transferred to the fetal circulation.

An interesting demonstration of the relationship that exists between fetal and maternal circulations has recently been presented before the French Academy of Science by Roux, wherein he has given an account of the work of Nathan-Larrier, Ramon and Grasset.[19] In certain regions of Africa where tetanus neonatorum still takes a large toll of death because of dirty scissors and unclean fingers, these authors have given injections to mothers a sufficient time before parturition of antitetanus anatoxin (toxoid). This injection into the mothers protects the newborn against tetanus for about two months during the most dangerous period, and Roux believes that this discovery will save thousands of infants.

Even while I was writing this paper, an infant (case 15), aged 7 months, was sent to me, whose mother had indulged excessively in wheat during pregnancy. Her infant developed eczema after wheat cereals were added to its diet; it showed positive skin reactions to the various proteins of wheat, so that I cannot escape what appears to me to be definite evidence that infants are potentially sensitized in the uterus.

I do not claim that all cases of food allergy in infants are brought about in this way, for Schloss and his co-workers [16] have shown that young infants can become sensitized after birth by the passage of proteins through the intestinal wall. Further, I cannot say definitely that in all cases in which the mother indulges excessively in foods during pregnancy the child will be born sensitive, for all persons do not become sensitized even when they are exposed to proteins. I have found this to be true even among guinea-pigs, which are easily made sensitive.

In spite of the fact that experimental evidence seems to be against the transfer of proteins through the breast milk, I cannot rid myself of

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18. Walzer, M.: Studies in Absorption of Undigested Proteins in Human Beings: 1. A Simple Method of Studying the Absorption of Undigested Protein, J. Immunol. **14**:143, 1927.

19. Nathan-Larrier, Ramon and Grasset, quoted by Roux: A Method of Protecting the New-Born Against Tetanus, Rev. Internat. de l'Enfant. **2**:1112, 1926.

the notion that Shannon's [9] premise may still be correct, in view of clinical evidence presented by Talbot and by O'Keefe as well as by myself,[20] namely, that a mother who partakes excessively of a particular food during the nursing period may pass this food in an unchanged state through the breast milk and thus affect the nursling, as has been shown to a slight extent in some of the foregoing cases. However, whether or not it will be shown at some future time that breast milk has this influence matters little for the present theory, for we have shown that the transfer of proteins may occur through the placenta; thus the breast milk is placed in a position of secondary and minor importance.

In conclusion, I would like to state that what I have endeavored to show is that under certain conditions an infant having a predisposition for allergy may become actively sensitized in utero through the mother's overindulgence in certain protein foods during her antepartum period, and that after birth, when the child comes in contact with this food for the first time, it will manifest some form of allergic phenomenon.

If this premise be correct, it is to be hoped that physicians in general, and obstetricians and pediatricians in particular, will make an effort to attempt to prevent the development of such cases of protein hypersensitiveness.

CONCLUSIONS

1. The placenta is permeable in human beings and in guinea-pigs.

2. Proteins may pass from the maternal to the fetal circulation through the placenta in the human being and in the guinea-pig.

3. The human fetus and the fetus of the guinea-pig can be actively sensitized in utero.

4. Proteins can enter the circulation in an unchanged state from the maternal intestinal tract and thereby gain entrance to the fetal circulation.

5. Therefore, under certain conditions an infant with a predisposition for allergy may become actively sensitized in utero because of the mother's overindulgence in certain protein foods during her antepartum period, and after birth, when coming in contact with this food for the first time, it will manifest some form of allergic phenomenon.

6. The foregoing facts present a new explanation for the development of allergy in certain infants.

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20. Talbot, F. B.: Eczema in Childhood, M. Clin. N. Amer. **1**:985, 1918. O'Keefe, E. S.: The Relation of Food to Infantile Eczema, Boston M. & S. J. **183**:569, 1920; Eczema in Breast Fed Baby and Protein Sensitization **185**: 194, 1921; A Dietary Consideration of Eczema and Asthma in Infancy and Childhood, J. A. M. A. **78**:482 (Feb. 18) 1922. Ratner, B.: Certain Aspects of Eczema and Asthma in Infancy and Childhood from the Standpoint of Allergy, M. Clin. N. Amer. **5**:815, 1922.

THE INFLUENCE OF FEEDING ON CERTAIN ACIDS IN THE FECES OF INFANTS

II. THE EFFECT OF AN EXCESS OF LACTOSE IN BREAST MILK AND IN MODIFIED COW'S MILK, WITH OBSERVATIONS ON A PARENTERAL INFECTION *

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In a previous communication,[1] we reported the influence of breast and modified cow's milk on the excretion of certain volatile acids in the feces of nurslings.

We found the excretion of the volatile fatty acids to be relatively constant in infants given breast milk and extremely variable in those fed on cow's milk. It was also apparent that on the average the stools of infants given cow's milk were much heavier than those of infants fed on breast milk and that the excretion of acid seemed to bear a closer relation to the weight of the former than to that of the latter. The striking feature was the finding of propionic acid in the feces of normal infants who were artificially fed. Almost without exception, propionic acid seemed an index of feeding with cow's milk.

In this work, we were glad to be able to confirm the observations of previous investigators [2] that the free acid is relatively constant in breast-fed infants and variable in bottle-fed infants and that formic acid preponderates in the stools of the former, while acetic acid predominates in those of the latter.

This paper deals with the following questions: Are the variations in the intestinal fermentations of the two mixtures due to quantitative

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1. Gerstley, J. R.; Wang, Chi Che; Boyden, R. E., and Wood, A. A.: The Influence of Feeding on Certain Acids in the Feces of Infants, Am. J. Dis. Child., **35**:580 (April) 1928.

2. Tisdall, F. F., and Brown, E. W.: Acidity of Infants' Stools, Am. J. Dis. Child. **27**:312 (April) 1924; New York State J. Med. **25**:152, 1925. Bosworth, A. W.; Wilder, H. K.; Blanchard, M. E.; Brown, E. W., and McCann: Studies on Infant Feeding, Am. J. Dis. Child. **23**:323 (April) 1922.

differences in their carbohydrate content? If so, what would be the effects of the addition of an excess of carbohydrate to each?

The same technic of feeding, of collecting specimens and of chemical analyses was employed in this series of experiments as has been already reported. Infants were fed on breast milk, on breast milk with an excess of lactose, on appropriate mixtures of cow's milk and on these mixtures with an excess of lactose. To avoid a hypothetic effect of the age of the child, the order of feeding was reversed in some experiments.

Our results are tabulated in tables 1 to 4, and for simplification typical periods are represented graphically in charts 1 to 6.

TABLE 1.—*The Effect of the Addition of Lactose to Breast Milk on the Excretion of Acids in the Feces in Case 1*

Age in Weeks	Date	Type of Food	Stools No.	Weight	Cubic Centimeters of Tenth-Normal Acid per 24 Hours		
					Formic	Acetic	Total Volatile
	1925						
4	10/27	Breast milk	6	48.1	8.6	40.8	49.4
5	11/ 5		6	51.2	26.0	29.4	55.4
6	11/10		4	27.1	13.5	35.6	49.1
	11/11		5	54.3	26.5	25.0	51.5
7	11/17	Breast milk, lactose 6%	3	44.3	37.8	14.5	52.3
	11/18		2	21.7	25.2	4.8	30.0
8	11/24		4	24.6	19.3	4.7	24.0
	11/25		6	45.6	34.6	11.3	45.9
9	12/ 2		6	59.7	27.1	24.0	51.1
	12/ 3		7	52.1	41.0	48.0	89.0
10	12/ 9	Breast milk	11	87.6	56.9	11.7	68.6
	12/10		7	65.2	28.9	15.1	44.0
11	12/16		2	23.1	19.5	14.7	34.2
12	12/22		4	65.9	32.7	15.7	48.4
13	1/1/26		1	26.1	26.6	21.0	50.6
	1/ 2		2	33.4	13.1	29.2	42.3
15	1/12	Breast milk, lactose 6%	4	75.6	35.7	38.6	74.3
	1/13		8	90.3	53.2	35.6	88.8
16	1/20		7	73.5	23.9	23.4	47.3
17	1/26	Breast milk, lactose 12%	9	81.5	39.0	37.4	76.4
	1/27		8	59.8	52.7	54.8	107.5
18	2/ 2		5	48.6	47.3	58.0	105.3
	2/ 3		3	38.5	42.7	58.7	101.4
19	2/ 9		3	59.9	40.7	22.2	62.9
	2/10		4	56.4	29.6	36.4	66.0

Chart 1 shows the acid output of infants on breast milk and on breast milk with the amount of lactose doubled. In the first phase of the experiment, one sees the acid output typical of infants who are breast fed. Formic and acetic acids are present; propionic acid is not demonstrable; the total output of volatile acid is not high, and the total free acid obtained by titration is within the limits of normal. The addition of a large quantity of lactose does not have a constant effect. Severe diarrhea does not result nor does the weight of the stools show decided change. Formic and acetic acids are unaffected, propionic acid does not appear, the total volatile acidity is unchanged and the total free acidity remains in about the same relation to the total volatile acidity.

TABLE 2.—*The Effect of the Addition of Lactose to Breast Milk on the Excretion of Acids in the Feces in Case 2*

Age in Weeks	Date	Type of Food	Stools No.	Weight	Cubic Centimeters of Tenth-Normal Acid per 24 Hours			
					Formic	Acetic	Total Volatile	Titratable
	1926							
6	3/23	Breast milk	1	22.0	8.2	36.5	44.7	20.8
10	4/20		2	41.9	6.8	61.4	68.2	21.2
	4/21		2	24.4	12.4	20.5	32.9	22.8
11	4/27	Breast milk, lactose 10%	3	64.9	40.4	47.5	87.9	97.3
	4/28		4	25.4	30.7	23.7	54.4	46.0
12	5/ 4		2	33.0	18.0	25.7	43.7	25.5
	5/ 5		4	43.0	33.8	79.7	113.5	95.5
13	5/11		1	28.1	17.8	28.2	46.0	36.2
	5/13		5	68.9	30.9	32.1	63.0	40.7
14	5/18	Breast milk	4	57.7	33.2	73.3	106.5	84.6
	5/19		4	24.7	27.5	40.2	67.7	158.3
15	5/26		2	56.4	42.1	84.3	126.4	72.5
16	6/ 2		1	50.2	28.5	34.6	63.1	29.6
	6/ 3		1	11.5	11.9	11.5	23.4	10.0
17	6/ 8		6	93.0	11.6	80.7	92.3	42.4
	6/ 9		2	45.1	17.5	55.5	73.0	38.4

TABLE 3.—*The Effect of the Addition of Lactose to Breast Milk and to Modified Cow's Milk on the Excretion of Acids in the Feces in Case 3*

Age in Weeks	Date	Type of Food	Stools No.	Weight	Cubic Centimeters of Tenth-Normal Acid per 24 Hours				
					Formic	Acetic	Propionic	Total Volatile	Titratable
	1926								
4	5/25	Cow's milk ½, water ½,	7	91.9	.....	148.9	6.7	155.6	86.0
6	6/ 9	lactose 5%	3	46.6	38.6	37.8	8.9	85.8	39.3
7	6/15		3	23.5	3.4	24.8	5.2	33.4	2.5
7	6/16		4	29.8	21.6	27.1	8.8	57.5	12.0
8	6/23		4	42.0	50.3	3.1	23.8	77.2	10.7
9	6/30	Cow's milk ½, water ½,	6	138.8	42.6	10.3	6.4	59.3	49.6
10	7/ 7	lactose 17%	3	42.1	0.7	78.4	3.5	82.5	58.2
	7/ 8		6	86.2	155.3	9.5	15.4	180.2	94.7
11	7/14	Cow's milk ½, water ½,	2	37.3	.....	36.5	25.5	62.0	28.5
13	7/22	lactose 5%	3	22.0	.....	24.3	10.7	34.9	42.1
	7/23		1	10.4	.....	14.4	3.5	17.9	39.0
15	8/ 5	Breast milk	1	26.2	19.7	75.0	....	94.7	118.2
	8/ 6		1	16.1	12.5	32.3	....	44.8	29.6
16	8/12		1	24.4	20.2	42.1	....	62.3	65.4
	8/13		1	18.6	19.0	26.0	....	45.0	47.5
17	8/19	Breast milk, lactose 12%	2	30.1	18.4	51.6	....	70.0	68.1
	8/20		1	11.9	5.9	13.4	....	19.4	9.3
18	8/26		3	34.7	24.4	58.0	....	82.5	83.3
19	9/ 2	Breast milk	1	30.7	5.5	70.4	....	75.9	53.4
	9/ 3		1	2.1	7.1	6.3	....	13.4	0.1
20	9/ 9		2	29.5	26.6	33.3	....	59.9	43.9
21	9/16	Cow's milk ⅔, water ⅓,	1	86.0	.....	118.6	....	118.6	75.0
22	9/23	lactose 6%	10	394.3	103.7	309.1	....	412.8	326.2
	9/24		9	273.9	168.4	392.7	....	561.2	506.3
23	9/30		6	118.1	82.6	103.3	....	185.9	100.0
	10/ 1		4	178.9	90.7	177.1	....	267.8	153.4
24	10/ 6		4	102.7	27.9	92.1	26.8	146.8	28.3
	10/ 8		5	217.4	55.8	87.3	56.0	199.1	11.6
25	10/13	Cow's milk ⅔, water ⅓,	2	86.5	62.7	45.4	9.0	117.1	44.6
	10/14	lactose 12%	2	91.5	45.4	78.1	17.5	141.0	45.1
26	10/20		3	73.6	18.0	107.4	trace	125.5	48.8
	10/21		4	111.0	66.5	115.5	16.4	198.4	125.1
27	10/27		2	50.2	25.8	36.8	30.2	92.8	9.9
	10/28		2	84.5	70.6	62.6	29.5	162.6	58.7
28	11/ 3		3	69.9	38.3	103.7	48.2	190.2	67.4
	11/ 4		2	47.0	12.0	72.1	1.6	85.6	42.8

These changes were so slight that we tried a more daring experiment. Chart 2 gives the results with the amount of lactose almost trebled. This great excess causes a slight relative increase in the acetic acid and also in the total volatile and total titratable acid, but this is manifested by the absence of diarrhea; and by the lack of a striking increase in either the number or the weight of the stools.

These experiments seem to indicate that in a normal baby an excess of lactose added to breast milk has little effect on the extent of carbohydrate fermentation in the intestine.

TABLE 4.—*The Effect of the Addition of Lactose to Breast Milk and to Modified Cow's Milk on the Excretion of Acids in the Feces in Case 4*

Age in Weeks	Date	Type of Food	Stools No.	Weight	Cubic Centimeters of Tenth-Normal Acid per 24 Hours				
					Formic	Acetic	Propionic	Total Volatile	Titratable
	1926								
4	11/24	Breast milk	5	54.5	76.1	23.9	....	100.0	39.4
5	11/30		4	61.1	39.0	40.6	....	79.6	49.0
	12/ 2		5	38.9	17.9	42.4	....	60.2	34.6
6	12/ 7		3	41.7	42.3	38.1	....	80.4	87.5
	12/ 9		5	64.9	46.2	19.4	....	65.6	40.0
7	12/14		4	33.8	22.7	14.4	....	37.1	17.2
	12/16		4	49.3	32.2	19.4	....	51.6	33.9
8	12/21	Breast milk, lactose 8%	7	107.3	42.3	82.5	....	124.8	64.7
9	12/28		6	91.0	40.1	58.3	....	98.4	47.7
	12/30		4	49.5	40.9	14.1	....	55.5	39.9
15	2/8/27	Cow's milk ⅔, water ⅓,	4	97.6	63.8	59.8	47.2	170.8	67.7
	2/10	lactose 5%	5	155.0	56.0	89.7	7.8	153.5	105.9
16	2/15		4	92.1	22.3	91.2	9.4	123.0	13.6
	2/17		2	50.4	3.6	76.5	25.6	105.7	8.0
17	2/22	Cow's milk ⅔, water ⅓,	5	100.8	26.6	141.3	3.3	171.3	124.6
	2/24	lactose 12%	6	110.3	49.9	101.0	5.8	156.7	108.8
18	3/ 1		5	100.7	46.9	64.3	8.8	120.0	93.3
	3/ 3		5	103.7	45.0	66.5	4.3	115.8	63.0
19	3/ 8		7	122.2	88.9	14.2	21.5	124.6	88.4
	3/10		4	110.1	44.9	70.2	3.4	118.6	52.8
20	3/15		4	56.6	45.0	57.7	8.8	111.5	70.0
	3/17		3	77.0	35.6	65.8	6.3	107.6	79.0
23	4/ 5	Cow's milk ⅔, water ⅓,	2	58.6	32.7	60.1	38.9	131.7	7.8
	4/ 7	lactose 5%	1	41.4	22.5	62.0	21.6	106.2	10.3

Chart 3 shows the experiments repeated in the medium of modified cow's milk. In the first phase, there is a typical picture seen in infants fed on cow's milk, namely, an excess of acetic acid over formic, the presence of propionic acid, a much higher total volatile and a much lower total free acid than in the breast-fed infant. The addition of 12 per cent lactose causes a slight increase in the output of formic acid. The increase in titratable acid is noticeable. There is a slight suppression of propionic acid. The number of stools as well as the weight of the stools is greatly increased, much more so than in the experiments on infants fed on breast milk. The withdrawal of excessive carbohydrate causes a return of the excretion of acid to normal. In this chart it will be seen that the relation of the titratable acidity to the total volatile acidity in a general way resembles the relations in the

breast-fed infants. In the feeding formula the relation of lactose to protein approximates that of breast milk. Does the amount of free acid independent of the amounts existing in various combinations depend on this relationship? This will be studied in later experiments.

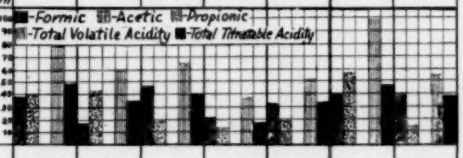
	Breast Milk					Breast Milk + 8% Lactose	
Date	11-30-'26	12-2-'26	12-9-'26	12-14-'26	12-16-'26	12-28-'26	12-30-'26
Age in weeks	5		6		7	9	
Feedings in Cubic cm	638	694	808	765	850	843	557
CC of Tenth Normal Sodium Hydrate							
No. of Stools	4	5	5	4	4	6	4
Weight of fresh stool in grams	61.1	38.9	64.9	33.8	49.3	91.0	49.5

Chart 1.—The effect of adding 8 per cent lactose to breast milk on the excretion of acids in the feces.

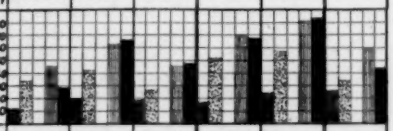
	Breast Milk			Breast Milk + 13 % Lactose		Breast Milk
Date	8-6-'26	8-12-'26	8-13-'26	8-19-'26	8-26-'26	9-9-'26
Age in weeks	15	16		17	18	20
Feedings in Cubic cm	850	850	850	765	793	907
CC-Tenth Normal Sodium Hydrate						
No. of Stools	1	1	1	2	3	2
Weight of fresh stool in grams	16.1	24.4	18.6	30.1	34.7	29.5

Chart 2.—The effect of adding 13 per cent lactose to breast milk on the excretion of acids in the feces.

It is evident that carbohydrate added in excess to modified cow's milk causes a greater change in intestinal fermentation than the same amount of carbohydrate added to breast milk.

With one exception, the infants remained clinically well and gained in weight during all these experimental periods. This case was so interesting and instructive that it is discussed in detail.

Charts 4 and 5 give the clinical record of this child. For about a week the baby had appeared a little below par, and then developed a mild bronchitis. Immediately diarrhea became acute, and the nutritional reaction of the child was that of a beginning alimentary intoxication. With no change of formula, the child automatically reduced the food intake and by the end of the week appeared perfectly well. Not having our chemical results as yet, his clinical condition easily permitted the continuation of the experiment. The addition of 12 per cent lactose did not cause a recurrence of the intestinal symptoms and resulted in a gain in weight. In a few days, the weight curve dropped temporarily but there was no associated diarrhea. Then it showed uninterrupted

⅔ Cows Milk 5% Lactose		⅔ Cows Milk 12% Lactose					⅔ Cows Milk 6% Lactose	
Date	2-15-'27	2-17-'27	2-24-'27	3-1-'27	3-3-'27	3-8-'27	3-10-'27	4-5-'27	4-6-'27
Age in weeks	16		17	18		19		23	
Feedings in Cubic cm	992·0	992·0	964·0	992·0	992·0	949·0	949·0	992·0	992·0
C C Tenth Normal Sodium Hydrate									
Number of Stools	4	2	6	5	5	7	4	2	1
Weight of fresh stool in grams	92·1	50·4	110·3	100·7	103·7	122·3	110·1	58·6	41·4

Chart 3.—The effect of adding 12 per cent lactose to a mixture of two-thirds cow's milk on the excretion of acids in the feces.

progress. Periods on the metabolism frame are indicated by the parallel lines.

Chart 6 gives the analyses in this case. Though at the time of the infection the diet contained only 6 per cent lactose, the effect of the bronchitis on the excretion of acid was remarkable. Under no other circumstances in our experiments did the amounts even remotely approach these. Associated with the great increase in formic and acetic acids is the disappearance of propionic acid. The unusual excretion of the total volatile and the free acid parallels the severe diarrhea and the greatly increased weight of the bowel movements.

During the weeks following, when the child was apparently well, the excretion of acid and the weight of the feces remained higher than normal, but even at this time the addition of 12 per cent lactose did not

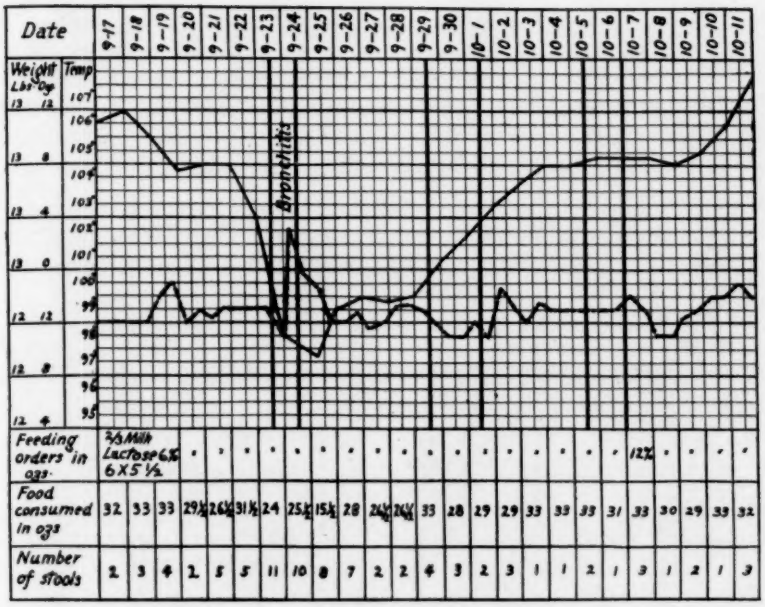


Chart 4.

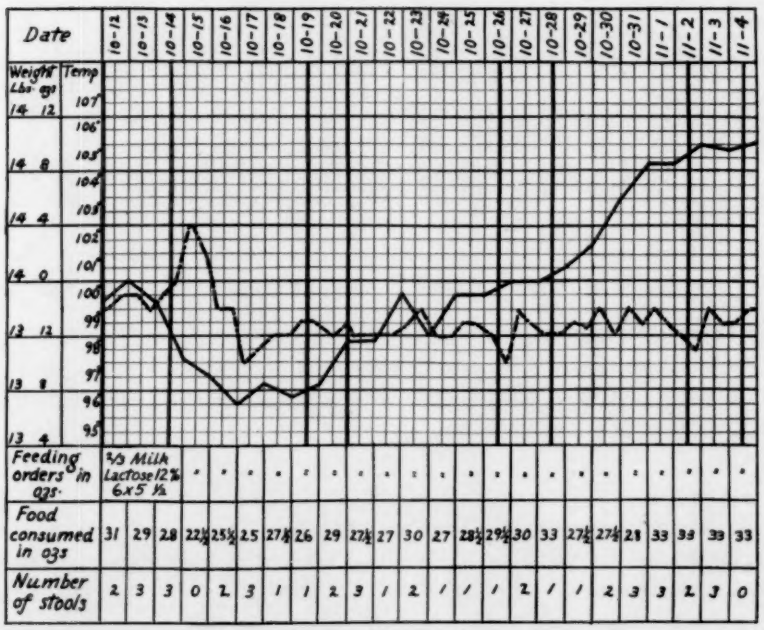


Chart 5.

Charts 4 and 5.—Clinical chart showing the effect of a bronchitis on the temperature, weight and number of stools in a baby on two-thirds milk with 6 per cent lactose. Increase of lactose to 12 per cent did not cause serious difficulty. The broken line shows the temperature curve; the unbroken, the weight curve.

cause an increase in the excretion of acid. The weight of the stools diminished, and the chart showed no great difference from that of the baby previously fed on cow's milk with 12 per cent lactose. Even at this time an excess of lactose did not precipitate a renewal of the disturbance.

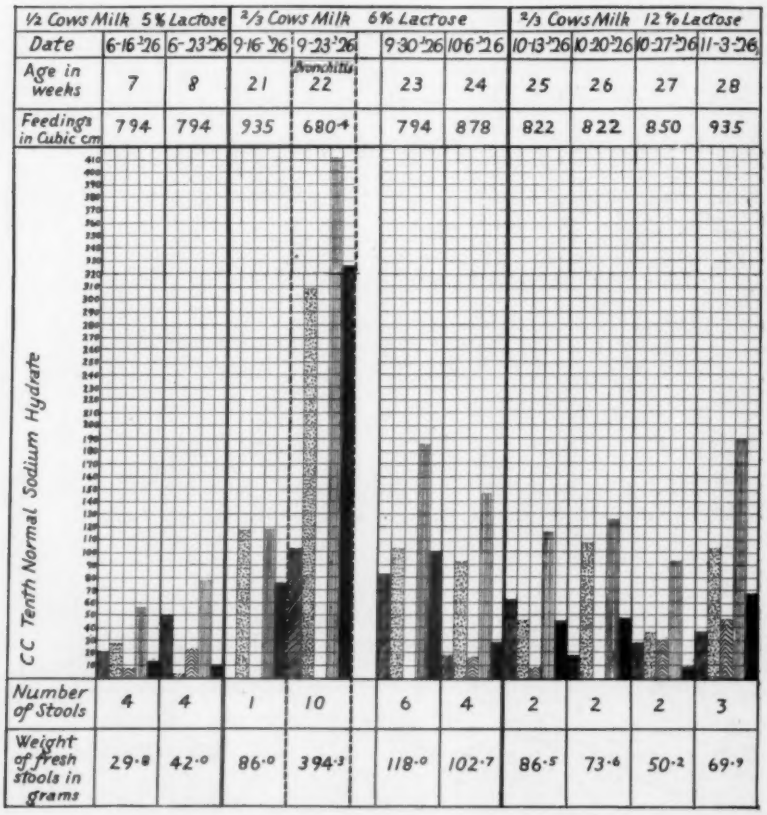


Chart 6.—The effect of a parenteral infection in a baby on two-thirds milk with 6 per cent lactose and later an increase of lactose to 12 per cent on the excretion of acids in the feces.

CONCLUSIONS

1. The addition of an excess of lactose to breast milk causes little change in the excretion of the volatile acids, the titratable acid or the weight of the stools.

2. The addition of an excess of lactose to mixtures of modified cow's milk causes only slight change in the total excretion of the volatile acids, though it does increase decidedly the amount of free acid. The frequency and weight of the stools are also affected.

The addition of 12 per cent lactose created a relationship of total titratable to total volatile acidity resembling that in breast milk. This may be due to the similar relations existing between lactose and protein in this formula.

3. An excess of lactose in either breast milk or cow's milk did not result in an immediate disturbance of nutrition.

4. An intercurrent bronchitis was a much more powerful factor in increasing the excretion of acid than any increase of carbohydrate in the mixtures.

5. Following such a parenteral infection, the excretion of acid remained high for some weeks, although the baby remained clinically well. The addition of an excess of lactose at this time did not cause an immediate disturbance.

6. These studies favor the Finkelstein hypothesis that intestinal fermentations are not primary but occur only after the development of some disturbance of nutrition.

BLOOD FAT IN DIABETIC CHILDREN*

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During the past three years, more than 400 determinations of blood fat have been made in eighty patients with diabetes attending the Hospital for Sick Children, Toronto. Bloor's [1] nephelometric method was used, and the determinations were made on the plasma. Ample figures for the normal blood fats of children have been furnished in the literature by Marriott and Sisson [2] and by Cowie and Hoag.[3] The former workers give 590 mg. of fat per hundred cubic centimeters of blood as the normal, and the latter, 700 mg. These figures vary little from those obtained by Bloor in normal adults.

Since the days when bleeding was in vogue as a universal therapeutic procedure, milkiness of the serum has been noted in persons with diabetes, and for more than a hundred years such milkiness has been attributed to increased fat content. Distinct turbidity of the blood plasma was noted in seventeen, or 21 per cent, of our patients. In others, a creamy layer would form over the surface of the blood if it were allowed to stand for an hour or so. The blood fat in these seventeen patients varied from 444 to 3,000 mg. per hundred cubic centimeters of blood. Milky serums were most frequently seen when fasting blood was withdrawn early in the morning. Not infrequently it was present at this time and absent later in the day, although the actual fat content had not altered appreciably. A correlation between the fat content and the turbidity of the serums was not possible, as not only were many lipemic serums clear, but lactescent serums were not always sufficiently rich in fat to be regarded as lipemic. Milky serums did not furnish evidence of the severity of the case. Our observations agree with those of White [4] that lactescence is merely an indication of the stability of the blood fats at the time of observation.

DETERMINATION OF INITIAL BLOOD FATS

The blood fats have been determined in twenty-four of the patients before the institution of any treatment. The results are given in table 1.

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* Received for publication, May 4, 1928.

* From the laboratories of the Subdepartment of Pediatrics, University of Toronto, the Hospital for Sick Children, and the wards of the Hospital for Sick Children.

1. Bloor, W. R.: J. Biol. Chem. **23**:317, 1915.
2. Marriott, W. McKim, and Sisson: Tr. Am. Pediat. Soc., 1918.
3. Cowie, D. M., and Hoag, L. A.: Studies in Blood Fat, J. A. M. A. **77**:1493 (Nov. 5) 1921.
4. White, A. C.: Quart. J. Med. **19**:159, 1926.

TABLE 1.—*Initial Blood Fat Content* *

Case	Date	Age	Blood Fat, Mg. per 100 Cc.	Blood Sugar, per Cent	Urine		Per Cent Abnormality of Weight	Comment
					Acetone	Diacetic		
W. D.	Aug., 1925	8	1,320	0.08	++	0	—20	Moderately severe; has done well on diet plus insulin
S. M.	Aug., 1925	6	1,320	0.357	+++	—	—13	Mild case; mentally defective; has become severe because uncooperative
I. P.	June, 1926	8	419	0.133	+	—	—21	Mild case; has done well on diet without insulin
R. C.	Jan., 1926	2	574	0.166	+	—	—10	Mild case; almost constantly aglycosuric on diet alone
B. P.	Feb., 1926	14	862	0.190	++	+	— 1	Moderately severe case; general condition good now
G. M.	Feb., 1926	2	1,646	0.330	++++	+	—15	Moderately severe; continues to improve on diet plus insulin
E. L.	March, 1926	9	2,820	0.440	++++	++	—22	Severe case; has improved greatly on diet plus insulin
J. W.	March, 1926	6	1,138	0.223	++	+	— 9	Mild case in 1926; moderately severe now because of frequent breaks
M. N.	Jan., 1926	14	396	0.200	+	0	0	Mild case; needed insulin at first; has improved greatly
E. D.	March, 1926	9	808	0.181	+	0	—10	Moderately severe; has always done well
M. B.	March, 1926	8	379	0.171	++	0	—18	Mild case; tuberculosis; has done well
A. M.	March, 1926	10	433	0.454	+++	+	....	Severe case; has done well on insulin plus diet
M. W.	April, 1926	9	3,528	0.450	++++	++	—10	Severe case; has done poorly because of failure to cooperate
J. D.	Sept., 1926	13	959	0.121	+	0	0	Mild case; has done well on diet alone
M. Bo.	Sept., 1926	10	2,222	0.190	+++	+	0	Severe case; comatose on admission; doing well now
B. G.	Sept., 1926	12	1,220	0.343	+++	+	— 8	Moderately severe; tuberculosis; does well when cooperating
M. We.	Oct., 1926	3	1,975	0.445	++++	+	—36	Severe case; does well on diet and insulin
L. M.	Jan., 1927	2	3,419	—	++++	++	—20	Admitted in coma; died
G. W.	Feb., 1927	10	739	0.277	+++	+	—21	Severe case; still needs large doses of insulin; poor cooperation
J. Wt.	Feb., 1927	8	756	0.250	++	+	—26	Moderately severe; doing fairly well on diet plus insulin
V. B.	Dec., 1927	8	1,000	0.380	+++	+	—15	Moderately severe; doing well on diet plus insulin
D. H.	Dec., 1927	5	800	0.200	++	+	— 2	Moderately severe; doing well on diet plus insulin
A. S.	Feb., 1926	2	888	0.190	++++	++	—20	In coma some days before admitted; temporary improvement; death
W. G.	Oct., 1926	12	2,730	0.130	++	+	—23	Just recovering from coma at time of test; doing well; insulin plus diet

* In estimating the degree of abnormality of weight in this study, the figures given by Brown and Tisdall (Common Procedures in Practice of Pediatrics, pp. 236-238, 1926) representing weight related to both height and weight were used.

In nineteen cases, or 79 per cent of those studied, the fat content of the blood was greater than normal. Eleven patients, or 46 per cent, had definite lipemia, i. e., more than 1,000 mg. of fat per hundred cubic centimeters of plasma. Most of the latter group were suffering from acidosis of some degree. Coma was constantly present in those with 2,000 or more mg. of fat per hundred cubic centimeters of plasma.

All patients with a definite lipemia before treatment was started have proved to be severely diabetic to the extent that they all require insulin to handle adequate diets. Some, however, require only small doses, whereas some who had low initial blood fats have since become severely diabetic.

The height of the initial blood fat when coma is present is apparently not of prognostic value. The lipoidemia rapidly disappears with treatment, e. g., in patients M. W. and M. We., it fell to normal within two weeks, at which level it remained until subsequent dietary indiscretion or infection caused lipemia to recur.

A consistent relationship between the initial weight and the initial blood fat is not apparent. The weights of the children studied varied from nearly 40 per cent underweight to normal. None were overweight. Such degrees of malnutrition might be considered sufficient to exert an effect on blood fats if the latter were influenced by undernutrition.

Our results do not indicate that initial blood fats in diabetes are such reliable guides in making a prognosis as Gray [5] and Blau and Nicholson [6] concluded from their studies. Four of those children whose initial blood fat exceeded 2,000 mg per hundred cubic centimeters have already outlived the two years' expectation of life allotted them by Gray. We have found that the initial blood fat is almost as unstable as the blood sugar. Definite lipemia depends on the presence of acidosis more than any other one factor. In the absence of acidosis greater weight may be attached to initially high blood fats in making a prognosis, but even then the latter must be guarded.

Blood fats offer little as a diagnostic aid in children. Absence of lipemia does not exclude diabetes, nor do moderate degrees indicate its presence. Marked lipemia is usually accompanied by sufficiently striking symptoms of diabetes that its presence is not needed to make the diagnosis. In the only patient with renal diabetes observed during this period, the blood fat was 1,045 mg. per hundred cubic centimeters of blood. Sugar tolerance curves and basal metabolic studies of this child ruled out the presence of diabetes, and his progress during the year and a half since the time of observation has confirmed the diagnosis of renal glycosuria.

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5. Gray, H.: Am. J. M. Sc. **35**:168 (July) 1924.

6. Blau, N. F., and Nicholson, S. F.: Fat Metabolism in Diabetes Mellitus, Arch. Int. Med. **26**:738 (Dec.) 1920.

An increased excretion of ketone bodies might reasonably be expected in patients with hyperlipoidemia. That such, in general, is true is shown in chart 1 in which the percentage of children with varying degrees of acetonuria had on the one hand normal blood fats and on the other definite lipemia, as indicated by a blood fat of 1,500 or more mg. per hundred cubic centimeters. Our observations do not, however, confirm those of Adler,[7] who stated that diabetic lipemia is always associated with acidosis. Five per cent of the patients without ketosis had definite

TABLE 2.—*Blood Fat in Persons with Severe Acidosis and Coma*

Name	Blood Fat, Mg. per 100 Cc.	Blood Sugar	Blood Acetone	Urine		Comment
				Acetone	Diacetic	
E. L.	2,820	444	+	++++	+	Blood taken before any treatment
	1,880	370	Trace	+	0	Blood 8 hours after 100 units of insulin plus dextrose
	1,242	530	+	++++	0	Blood 8 hours after foregoing sample
M. W.	2,666	464	+++	++++	+	Before any treatment
	3,333	430	++	+++	0	Four and one-half hours after 80 units of insulin plus dextrose
	3,028	360	Trace	++	0	Four hours after second sample
	2,666	100	Neg.	Neg.	0	Twenty-four hours after starting treatment with insulin plus dextrose
M. We.	3,628	450	+++	+++++	++	Before any treatment
	3,418	420	++	+++	0	Three hours after 80 units of insulin plus dextrose
	2,222	200	+	+++	0	Fourth day after starting treatment
B. M.	3,419	400	+	+++	++	Untreated coma; died in a few hours
S. M.	1,320	357	+	+++	+	Severe acidosis
A. M.	4,336	454	++	++++	+	Coma; recovery
M. W.	1,975	445	+	++++	+	Coma; recovery
G. W.	888	277	+	+++	+	Severe acidosis; pneumonia; recovery
G. M.	1,646	330	+	++++	+	Coma; recovered
M. B.	2,222	196	+++	+++++	+	Coma; recovery; blood taken 4 hours after insulin
B. G.	1,220	343	+	++++	+	Severe acidosis; recovery
W. G.	2,730	130	0	++	+	Just recovering from coma; treated with insulin
V. B.	1,600	380	Trace	+++	+	Severe acidosis; recovery
F. S.	3,800	550	++	+++++	++	Untreated coma; died

lipemia. The converse of this statement proved more nearly true in our cases, as 83.4 per cent of patients excreting large amounts of acetone had lipemia, while none had a normal amount of blood fat.

Acidosis of sufficient severity to produce clinical symptoms of acidosis or coma is usually accompanied by hyperlipoidemia, as is shown in chart 1. The rate of fall of blood fat concentration after institution of suitable insulin therapy varies considerably, but usually requires weeks for the blood fat to reach its previous height or a stationary level. The qualitative tests for acetone are readily made and kept negative by treatment, in spite of the persistence of marked elevation of blood lipoid

7. Adler, M.: Berl. klin. Wchnschr. **46**:1453, 1909.

content. Such rises of blood fat as accompany coma may be marked, and yet after the acidosis is removed the blood fat falls to normal or nearly so, and the child progresses well on suitable treatment.

Rapid increase of blood lipoids over their previous level at times warns of approaching acidosis, even in the absence of other signs or symptoms. For example, the blood fat of A. G., who reported frequently to the clinic, varied from 900 to 1,000 mg. per hundred cubic centimeters over a period of eighteen months. On Jan. 28, 1927, he reported for routine examination. The blood sugar was 0.205 per cent; the blood fat, for some inexplicable reason, had risen to 2,539. Twenty-four hours later he suddenly developed symptoms of severe acidosis, which demanded urgent treatment, Blood fat returned to its previous level after a few weeks' treatment.

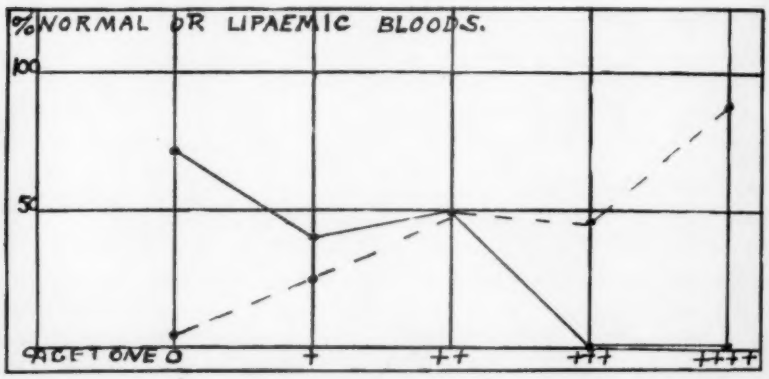

Chart 1.—Blood fat and acetonuria. The solid line indicates normal blood fat and the broken line, blood fat over 1,500.

Most observers have been unable to demonstrate any constant relationship between blood sugar and blood fat. Both Bang [8] and Wishart [9] concluded from their studies that consistent deviations of the two from normal did not exist. Our observations are plotted in chart 2. It would appear that in general they do vary in the same direction. Such an observation must be qualified by the statement that, as Gray pointed out, the parallelism is more apparent in the average than in individual cases, which provide many exceptions. Definite lipemia associated with low or normal blood sugar was usually seen with either oncoming or disappearing acidosis, when the hyperglycemia is eradicated more quickly than hyperlipoidemia. Lipemia of moderate degree is sometimes present

8. Bang, I.: Biochem. Ztschr. **94**:359, 1919.
9. Wishart, M. B.: J. Metab. Research **2**:199, 1922.

in patients with mild cases of diabetes whose blood sugar is being maintained practically constantly at a normal level.

The relationship between carbohydrate metabolism and blood fat might possibly be better studied by observing the effect of gains or losses of tolerance rather than by the study of coincident blood sugar. Improvement in tolerance has, in our experience, usually meant maintenance of a nearly normal blood sugar, and failure to gain in tolerance has almost invariably been the result of frequent or persistent hyperglycemia. In table 3 are given a number of the results obtained by such a study.

Improvement in tolerance usually resulted in maintenance of the blood fat at a normal level or, in patients with an initial lipemia, in a reduction of the latter to a lower or even normal level. In most of

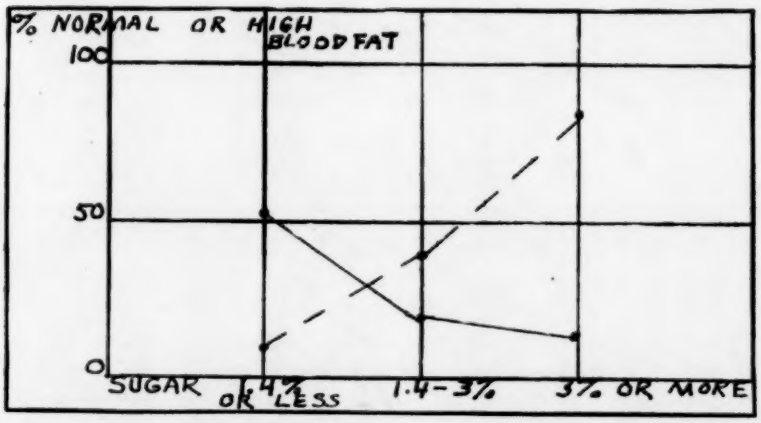

Chart 2.—Blood fat and blood sugar. The solid line indicates normal blood fat and the broken line, lipemia.

those patients with a stationary or decreased tolerance, the amount of blood fat remained high or even increased. Such observations are, however, applicable only in general, fluctuations in plasma lipoids occurring readily and increases usually persisting some time after the periods of glycosuria which have induced them have cleared up. Seemingly, even severe cases show improvement when the patient is under control for a few months, and thereby furnish apparent discrepancies to the generalization already stated. For example, M. W. showed a decreasing tolerance but apparent maintenance of a low blood fat. The explanation is that the studies in this case were all made after stays in the hospital, during which time the tolerance showed temporary improvement. The one time that blood was obtained before hospitalization, hyperlipoidemia was present.

TABLE 3.—*Blood Fat and Tolerance*

Case	Date	Age	Blood Fat, Mg. per 100 Cc.	Tolerance*	Per Cent Abnormality of Weight	Comment
M. N.	Jan., 1926	13	396	0.8	0	Practically never any glycosuria; took insulin six months, then diet alone
	Dec., 1926	14	608	0	— 8	
T. B.	Feb., 1923	8	1,111	0.64	— 1	Practically always aglycosuric; occasionally slight increases in blood sugar
	Sept., 1926	8½	1,050	0.72	0	
S. H.	June, 1925	9	200	2.80	+ 1	This determination followed three months of aglycosuria and reduction in insulin
	Jan., 1926	9½	555	1.80	+ 8	Aglycosuric most of time
G. A.	Dec., 1925	12	359.8	0.37	+10	Patient always aglycosuric but because of high renal threshold, blood sugar sometimes increased and possibly missed
	March, 1926	12¼	683	0.41	+10	
	Nov., 1926	13	1,777	0.54	+ 1	
	Nov., 1927	14	785	0	0	Frequent blood sugars always normal
N. D.	April, 1926	12	523	C 142	+ 2	Almost constantly aglycosuric
	June, 1926	12	608	C 157	....	Frequent blood sugars normal
	Oct., 1926	12½	493	C 157	+ 2	
	Sept., 1927	13½	500	C 172	+ 4	
S. A.	June, 1925	10	469	0.68	— 5.9	Fairly mild case; requiring only small doses of insulin
	Aug., 1926	11	746	0.70	—16	Usually sugar-free
B. D.	Nov., 1926	6½	1,481	C 105	—10	Mild case, easly controlled by diet alone
	Dec., 1926	6½	1,164	C 125	— 8	
P. B.	June, 1925	7	660	1.8	....	Aglycosuric most of time but had periods of glycosuria with temporary need of more insulin every few months
	Jan., 1926	7½	592	1.8	+ 5	
	June, 1926	8	608	1.8	+ 5	
R. M.	June, 1925	10	549	1.9	+ 1	Severe case; cooperative and showing real improvement until July, 1925; frequent glycosuria thereafter
	Sept., 1925	10½	1,189	4.6	+ 3	
	Feb., 1926	11	987.6	4.4	+ 7	
M. W.	July, 1925	12	860	2.5	— 2	Cooperative during this period and sugar-free most of time
	Nov., 1925	12½	592	2.8	0	
	March, 1926	13	2,666	(coma)		For some months previous to this had glycosuria most of time; now cooperative; last three figures obtained after periods of forced control while in hospital
	May, 1926	13	603	3.4	0	
	Nov., 1926	13½	555	4.3	— 1	
N. A.	July, 1925	12	660	4.9	—18	Severe case; patient cooperative at first; later, careless and had glycosuria often with frequent attacks of acidosis
	Aug., 1925	12	660	4.9	— 4.5	
	April, 1926	12¾	760	4.9	—18	
	Oct., 1926	13	1,185	4.1	— 5	
A. G.	June, 1925	13	470	1.2	+ 8	Severe case; cooperation good but hyperglycemia was frequent, and severe acidosis developed readily; marked tendency to obesity
	Jan., 1926	13½	480	1.3	+20	
	April, 1926	13¾	716	1.5	+15	
	May, 1926	13¾	962	1.5	....	
	Nov., 1926	14	1,048	2.5	+18	
	Jan., 1927	14½	2,539	2.6	....	
	Feb., 1927	14½	888	2.6	+10	
J. W.	Nov., 1925	5¾	1,481	0.72	— 8	Glycosuria plus slight acidosis at times; fairly well controlled since February, 1926
	March, 1926	6	1,139	2.6	—10	
	April, 1926	6	681	2.3	— 4	
Mi. B.	April, 1926	8	975	C 124	—18	Mild diabetes easily controlled
	June, 1926	8	1,316	C 134	— 7	Mediastinal tuberculosis
	Nov., 1926	8½	555	C 154	— 7	
J. H.	May, 1926	8	2,185	C 133	— 2	Mild case controlled by diet; almost constantly aglycosuric
	Oct., 1926	8½	375	C 133	+ 3	
	Jan., 1927	9	328	C 143	+ 8	
	Feb., 1928	10	340	C 178	+ 5	

TABLE 3.—*Blood Fat and Tolerance—Continued*

Case	Date	Age	Blood Fat, Mg. per 100 Cc.	Tolerance*	Per Cent Abnormality of Weight	Comment
M. M.	June, 1925	9½	738	C 117	— 6	Mild case controlled by diet alone; glycosuria for about one week prior to test April 26; sugar-free practically constantly except for foregoing period
	April, 1926	10	1,111	C 117	+ 3	
	Sept., 1926	10½	987	C 135	+ 5	
	Jan., 1927	11	522	C 148	0	
S. M.	Nov., 1925	6	1,111	3.3	+18	Severe case; cooperative and fairly well controlled during this period
	March, 1926	6½	935	2.5	+20	
F. M.	Nov., 1925	8½	1,111	4.2	+18	Severe case; aglycosuric and doing well until March, 1926, since then never sugar-free for whole day
	Feb., 1926	9	935	2.6	+20	
W. W.	Nov., 1925	3	1,147	2.1	+11	Moderately severe case; nearly always sugar-free during this period
	Feb., 1926	3½	421	2.5	+10	
B. P.	April, 1926	14	573	4.7	— 1	Cooperative; sugar-free most of time
	June, 1926	14	339	4.7	— 6	
	Sept., 1926	14½	2,091	4.7	— 7	Glycosuria unchecked for 2 or 3 mos.
	Oct., 1926	14½	1,367	2.6	— 5	Aglycosuria for 2 months

* The figures given under tolerance indicate the number of units of insulin required for each 10 Gm. of carbohydrate in the diet to keep the blood sugar normal. In the case of those patients not requiring insulin, the figure after the C indicates the total number of grams of carbohydrate the patient could tolerate at the time of the study.

EFFECT OF HIGH FAT DIETS ON BLOOD FATS

Since high fat diets have been in vogue in treating persons with diabetes, many workers have studied their effect on the blood fat. Bloor [10] stated that when fats supply more than 80 per cent of the energy intake, the factor of incomplete combustion of fats and production of acetone bodies becomes a source of danger. As modern diabetic diets often approach or exceed this amount, ill effects might be expected to follow their use. Most observers, however, have failed to find such ill effects indicated by any increase in the blood fat. Bang [11] showed that habituation to high fat diets reduced lipemia in both dogs and man, and he later [8] studied twenty-three diabetic persons who had been placed on high fat diets from Petren's clinic and regarded any large amounts of blood fat encountered as due to liver insufficiency. Blatherwick [12] analyzed the blood fat of patients on Newburgh diets and demonstrated that those with mild or moderately severe diabetes were able to utilize satisfactorily the large amounts of fat such diets contained. Newburgh and Marsh [13] used diets with a F.A.-G. ratio [14] of 2.5:1 (or even 4:1) without producing acidosis. They concluded that hyperlipoidemia is not produced by a diet rich in fats in those patients who do not already have

10. Bloor, W. R.: J. Metab. Research **4**:549, 1923.

11. Bang, I.: Biochem. Ztschr. **91**:111, 1918.

12. Blatherwick, N. R.: J. Biol. Chem. **49**:193, 1921.

13. Newburgh, L. H., and Marsh, P. L.: High Fat Diet in Treatment of Diabetes Mellitus, Arch. Int. Med. **31**:455 (April) 1923.

14. F.A.-G. = 90 per cent of fat + 46 per cent of protein; 10 per cent of fat + 100 per cent of dextrose + 58 per cent of protein.

TABLE 4.—*Blood Fat and Diet*

Case	Date: Mo.	Date: Year	Age	Blood Fat, Mg. per 100 Cc.	Diet: Per Cent Energy From Fat*	Diet: Ratio F. A. / G†	Calories per Lb.	Per Cent Abnormality of Weight	Comment
1. M. N.	1	1926	13½	396	76	1.6 : 1	21	0	Mild case; required insulin six months; then did well on diet alone
	12	1926	14	608	69	1.2 : 1	21	— 8	
2. N. A.	7	1925	12	660	75	1.45 : 1	31	—18	Severe case; periods of cooperation and improvement alternated with periods of glycosuria and acetonuria
	8	1925	12	666	75	1.45 : 1	25	— 4.5	
	4	1926	12¾	706	79	1.4 : 1	27	—18	
	10	1926	13	1,185	79	1.4 : 1	22.5	— 5	
3. J. H.	4	1926	8	1,247	69	1 : 1	31	—10	Mild case controlled by diet alone; never glycosuric since starting treatment; blood sugars usually normal
	5	1926	8	2,185	69	1 : 1	31	—10	
	10	1926	8½	378	69	1 : 1	31	+ 3	
	1	1927	9	328	68	0.8 : 1	27	+ 4	
	3	1928	10	340	63.5	0.8 : 1	27	+ 5	
4. B. P.	4	1926	13	573	74	1.4 : 1	21	— 1	Severe case; during this period no glycosuria or acidosis
	6	1926	13	339	70	1.14 : 1	17	— 7	
	9	1926	13½	2,091	70	1.14 : 1	18	— 7	During summer months ate general diet; constant glycosuria
	10	1926	13½	1,367	69	1.24 : 1	17	— 4	Sugar-free 1 month before test
5. J. W.	11	1925	5¾	1,481	75	1.4 : 1	43	— 9	Mild at first; became severe because of lack of cooperation
	3	1926	6	1,139	70	1.2 : 1	39	—11	
	4	1926	6	681	70	1.2 : 1	36	— 4	
6. M. M.	6	1925	9½	734	76	1.48 : 1	37	— 6	Mild case easily controlled by diet; practically always sugar-free after institution of treatment except for period of 10 days prior to test of April, 1926
	2	1926	10	606	76	1.48 : 1	31	0	
	4	1926	10	1,111	76	1.48 : 1	30	+ 3	
	5	1926	10¼	1,333	76	1.48 : 1	30	+ 3	
	9	1926	10½	987	74	1.25 : 1	29	+ 5	
	1	1927	11	522	71	1:15 : 1	30	0	
7. S. M.	9	1925	6	1,320	69	1.36 : 1	42	—12	Severe case; favorable progress during this period
	3	1926	6½	432	69	1.36 : 1	36	+20	
8. F. M.	11	1925	8½	1,111	74	1.4 : 1	28	+18	Severe case; difficult to control
	2	1926	9	935	74	1.4 : 1	27	+11	
9. W. W.	11	1925	3	1,147	69	1.1 : 1	30	+11	Fairly severe case; frequent glycosuria
	3	1926	3½	421	67	1 : 1	33	+12	
10. T. B.	2	1926	8	1,111	74	1.26 : 1	36	0	Fairly mild case requiring only small doses of insulin; almost constantly sugar-free
	9	1926	8½	1,050	70	1.25 : 1	35	0	
	10	1927	9½	980	72	1.2 : 1	33	0	
11. W. D.	8	1925	8	1,320	74	1.4 : 1	35	—20	Moderately severe case; well controlled and increasing tolerance
	8	1925	8	1,490	74	1.4 : 1	25	—20	
	8	1925	8	1,110	74	1.4 : 1	33	—10	
	11	1925	8	630	74	1.4 : 1	30	— 6	
	2	1926	8½	683	74	1.4 : 1	31	— 7	
12. A. G.	6	1925	13	470	73	1.35 : 1	24	+ 8	Severe case; cooperative; usually aglycosuric but frequent mild degree of hyperglycemia; tends to gain weight rapidly and easily; steady slow decrease in tolerance; severe acidosis twenty-four hours after test of January, 1927
	7	1925	13	478	73	1.35 : 1	22	+20	
	1	1926	13½	480	73	1.35 : 1	20	+15	
	4	1926	13¾	716	73	1.35 : 1	21		
	5	1926	13¾	962	73	1.35 : 1	21	+18	
	6	1926	13¾	955.7	73	1.35 : 1			
	11	1926	14	1,048	74	1.3 : 1	28	+10	
	1	1927	14	2,539	74	1.3 : 1			
	2	1927	14½	888	74	1.3 : 1			
13. G. A.	12	1925	12	359.8	79	1.6 : 1	27	— 1	Fairly mild case requiring only small dose of insulin; after 3 years able to discontinue insulin
	3	1926	12¼	683.9	64	1.2 : 1	27	— 1	
	11	1926	13	1,777	63	1 : 1	27	— 4	
	11	1927	14	785	64	1.1 : 1	24	0	
14. P. B.	6	1925	7	666	75	1.35 : 1	..	....	Moderately severe case; usually aglycosuric but frequent breaks of a few days' duration
	6	1925	7	1,369	75	1.35 : 1			
	1	1926	7½	592	75	1.3 : 1	29	+ 6	

TABLE 4.—*Blood Fat and Diet—Continued*

Case	Date Mo.	Date Year	Age	Blood Fat, Mg. per 100 Cc.	Diet: Per Cent Energy From Fat*	Diet: Ratio F. A. / G †	Calories per Lb.	Per Cent Abnormality of Weight	Comment
15. S. A.	6	1925	10	469	78	1.5 : 1	32	— 5.8	Mild, requiring only small dose of insulin; usually aglycosuric
	8	1926	11	746	78	1.5 : 1	31	—16	
16. R. M.	6	1925	10	549	79	1.4 : 1	22	+ 1	Severe case; cooperative and aglycosuric until July, 1925; subsequently frequent glycosuria
	9	1925	10½	1,189	79	1.4 : 1	21	+ 4	
	2	1926	11	987	79	1.4 : 1	19	+ 7	
17. M. W.	7	1925	12	869	75	1.45 : 1	26	0	Severe case; well controlled and aglycosuric until end of 1925; thereafter, no cooperation; almost constant glycosuria; comatose at test of March, 1926
	11	1925	12½	502	75	1.45 : 1	25	0	
	3	1926	13	2,262	75	1.45 : 1	32	—12	
	5	1926	13	603	75	1.45 : 1	28	0	
	11	1926	13½	555	69	1.24 : 1			
18. S. H.	6	1925	8	2,000	76	1.45 : 1	31	0	Severe case never adequately controlled
	1	1926	8½	555	76	1.45 : 1	29	+ 2	
19. F. Z.	6	1925	10½	635	70	1.3 : 1	29	+13	Constant hyperglycemia and frequent acidosis
	3	1926	11½	1,180		General diet		+ 9	
20. M. B.	3	1926	8	370.3	77	1.3 : 1	47	—20	Mild case complicated by mediastinal tuberculosis; almost constantly aglycosuric
	4	1926	8	975.6	77	1.3 : 1	47	—18	
	6	1926	8	1,316	70	1.16 : 1	42	— 7	
	11	1926	8½	555	67	0.9 : 1	48	— 7	
21. N. D.	4	1926	12	523	79	1.5 : 1	30	+ 2	Mild case controlled by diet alone; practically always aglycosuric
	6	1926	12	608	74	1.4 : 1	29	+ 2	
	10	1926	12½	493	72	1.16 : 1	28	+ 2	
	9	1927	13½	500	70	1 : 1	27	+ 4	
22. B. D.	11	1926	6½	1,481	73	1.28 : 1	37	— 8	Mild case; easily controlled by diet alone
	12	1926	6½	470	69	1 : 1	39	— 6	
23. J. D.	9	1926	13	959		Ward diet		0	Mild case; almost constantly sugar-free on diet
	10	1926	13	578	69	1.5 : 1	24	— 2	
	7	1927	14	600	76	1.45 : 1	24	— 9	
24. A. M.	5	1926	12	433.6	High carbohydrate			—10	Severe case; sugar-free on diet plus insulin 5 weeks before second test
	6	1926	12	502.1	72	1.45 : 1	31	— 4	
25. M. W.	4	1926	11	362.8	72	1.45 : 1	31	—10	Severe case; sugar-free during this period
	6	1926	11	592.5	72	1.45 : 1	31	— 4	
26. E. L.	3	1926	9¾	2,820	Dextrose only			—34	Severe case; coma, first test; sugar-free 3 weeks before second test
	4	1926	9¾	370	73	1.3 : 1	39	—28	

* Per cent of energy from fat equals that supplied by actual fat in the diet.

† $\frac{\text{F. A.}}{\text{G}}$ ratio $= \frac{\text{90\% fat + 40\% protein}}{\text{100\% of carbohydrate + 10\% of fat + 58\% of the protein}}$ of the diet.

it, and that an existing lipemia gradually falls. Wishart offered an only partially dissenting voice when she stated that severe diabetes and high fat diets are conducive to the development of lipemia.

Our interest in the fats contained in the blood was first stimulated by the observation that children on high fat diets, a ratio of 1.5:1, frequently developed anorexia and ketosis, after being on such diets for several months. It appeared and the earlier cases lent support to the view, that developing lipemia might be responsible for the symptoms. The diets I used scarcely ever exceeded F.A.-G. ratios of 1.5:1. Not

more than 75 or 80 per cent of the energy value of these diets is derived from fat. Most children taking such diets appear to be constantly on the borderline of ketosis, and insignificant factors produce acetonuria. It would therefore appear that these diets are disadvantageous in the treatment of the youthful diabetic patient, whose age and disease both tend readily to produce acidosis from minor disturbances. For these reasons, the proportion of carbohydrate in the diet has been increased with beneficial clinical results.

In table 4 are given the results of the observations of the blood fat in relation to food fat. A constant effect on the blood lipoids is not evident from the use of high fat diets, when the diabetes is adequately controlled by the diet or by diet plus insulin. The former, controlled by diet alone, showed a somewhat greater readiness to the production of lipemia than the latter, and the lipemia responded more promptly to reduction of the fat in the diet by lowering of the blood fat, e. g., in patients M. M., J. H. and M. N. One patient (M. M.) did develop seeming lipemia on high fat diets and responded to a larger proportion of carbohydrate by a reduction in blood fats. Attention to other details about the case shows that the rise in blood fats followed a period of glycosuria. In other cases in which the condition was adequately controlled, e. g., W. D., a progressive decrease of blood fat to a normal level, despite the continuance of the high fat diet, is noted. At most one might conclude from these figures that high fat diets produce lipemia and acidosis more readily when inadequate control of the case is maintained or infection supervenes, whereas in those patients with nearly constant aglycosuria and increasing tolerance, ill effects of high fat diets are not indicated by a study of the blood fats, even although such patients do better clinically on more carbohydrate and develop ketosis less easily when the F.A.-G. ratio does not exceed 1 : 1.

The most effective single factor in the diet in producing lipemia would appear to be excessive caloric intake. This applies when the energy intake is sufficient to produce rapid gain in weight or persistence of more than 10 per cent overweight in a child, irrespective of the fact that the same number of calories might be fed to another person without producing such an effect. In practically all the cases studied the patients were receiving twice their basal energy requirement, which met the demands in most cases without producing overweight, but in certain ones, e. g., A. G., tended to produce obesity.

Variations in the weight of the child from 10 per cent or more underweight to normal or a little over did not exert a consistent effect on the blood fat. Plasma studied during periods of rapid gain frequently showed some increase in lipoid content. Lipemia is usually present when the patient is 10 per cent or more overweight.

SUMMARY

1. A constant relationship does not exist between blood fat and the presence of turbidity of the serum.

2. In 70 per cent of the subjects studied, the initial blood fat was above normal. An initially high fat content of the blood in cases uncomplicated by acidosis is of some slight value in making a prognosis.

3. Lipemia is almost constantly present in patients with marked ketosis. It occurs in only a small number of patients in whom acetonuria is not present.

4. Severe acidosis and coma are always accompanied by hyperlipoidemia.

5. Rapid increase of blood lipoid suggests incomplete fat combustion and oncoming acidosis, even in the absence of suggestive symptoms or other signs.

6. Blood sugar and blood fat do not show any constant relationship to one another in individual cases, but on the average they parallel one another in their variations from the normal.

7. Increasing tolerance indicating a more or less constantly normal blood sugar usually results in maintenance of the blood fat at a normal level or a reduction of a preexisting lipemia.

8. A constant relationship does not exist between the fat in the diet and the blood fat when the F.A.-G. ratio does not exceed 1.5 : 1.

9. High caloric diets, or those sufficient to produce overweight tend to produce lipemia.

10. The state of nutrition affected the fat content of the blood only during periods of rapid gain or when the weight was constantly 10 per cent or more over normal.

RICKETS IN DOGS AS PROBABLY RELATED TO SEX *

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It is becoming more and more apparent from various studies on growth and metabolism that the two sexes must be thought of as responding differently to the same environmental conditions. As this knowledge becomes more detailed, and more delicate means of analysis are devised, probably the chemical constitutions of the male and female mammal will be accurately differentiated. From this point of view, I should like to record a rather simple case which has recently come under observation.

A number of dogs were bred under carefully regulated conditions and a striking difference between the development of rickets in males and females was found. An American fox-hound bitch whelped eight pups on Oct. 19, 1926. She was an excellent mother and nursed and cared for the pups in a normal manner. There were four males and four females in the litter. One male died when 2 days old from an unknown cause and one female died when 2 months old, apparently as the result of intestinal worms. Six animals, three males and three females, survived to full growth and maturity and all were kept living until past 1 year of age.

The six dogs, of course, were full sisters and brothers, whelped and nursed by the same mother and sired by the same father. The members of the litter were of one general type and pattern, showing a straight bred American fox-hound ancestry. The six pups were apparently normal when 10 weeks old so far as size and body form would indicate. After they were 10 weeks of age, and before reaching 3 months, the three male pups showed enlargements on the distal ends of the radius and ulnar and the typically deformed wrist and bent foreleg of a rachitic animal. One female showed the same condition to a mild extent, but the other two females did not show any trace of the disease. From this time on, the rachitic condition of the three males grew more pronounced until two of them were deformed and bandy-legged and the third showed distinct enlargements and knobbed bones (fig. 1). The one affected female presented about the same condition as did the most normal male, while the other two females grew to be straight slender-legged, beautiful fox-hounds (fig. 2).

The six animals were continually in the same whelping kennel while pups and were constantly fed on the same food. The six pups also received cod liver oil almost daily during their first three months of life.

These dogs were born at a particularly unfavorable season for exposure to direct sunlight, since at the time when they were sufficiently old to be placed outdoors the winter was so severe that they could not withstand the cold, and the cloudy dark season made sunshine scarce at any time.

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In spite of their uniform experience in diet and surroundings, the bone development of the three female pups was indubitably superior to that of the three male dogs; and since the diet and external conditions were equal at all times, the sex difference in bone growth seems probably due to some internal difference as a cause.

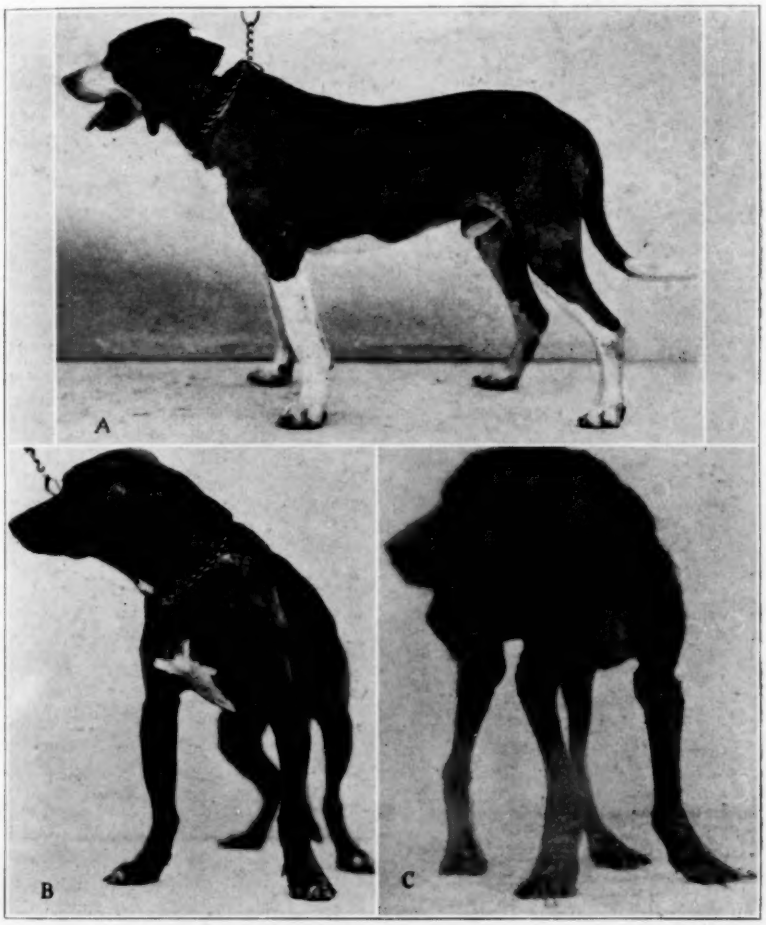

Fig. 1.—*A* is an American fox-hound male, showing knobbed wrists and mild symptoms of rickets. *B* and *C* show two male fox-hounds, with extremely pronounced rickets. The three dogs were litter mate brothers of the three bitches shown in figure 2 and their more decidedly rachitic condition is obvious.

I am led to believe that the superior condition of the three females as compared with the three male dogs is due to a generally better or more efficient calcium metabolism on the part of the female mammal. This sex advantage seems to give a better and more normal growth to

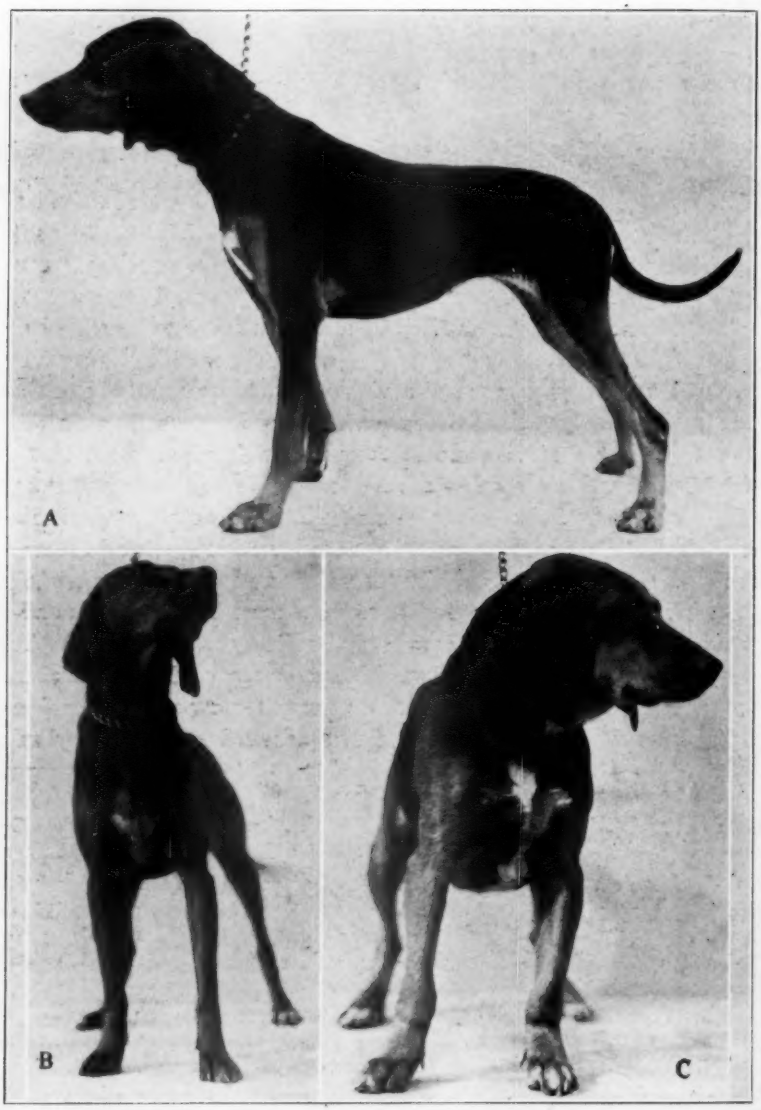

Fig. 2.—Three female litter sister fox-hounds, showing a perfect development of leg form in *A* and *B* and rickets in *C*. The condition of these three animals is far superior to that of their three litter mate brothers shown in figure 1.

the female of such large breeds as the St. Bernard dog which show huge overgrowth and probably acromegalia. It is apparently true that acromegalia is rarer and less pronounced in the human female than in the male. Even among lower vertebrates, as Hess [1] has recently found in the cod fish, the female seems to have a calcium advantage over the male.

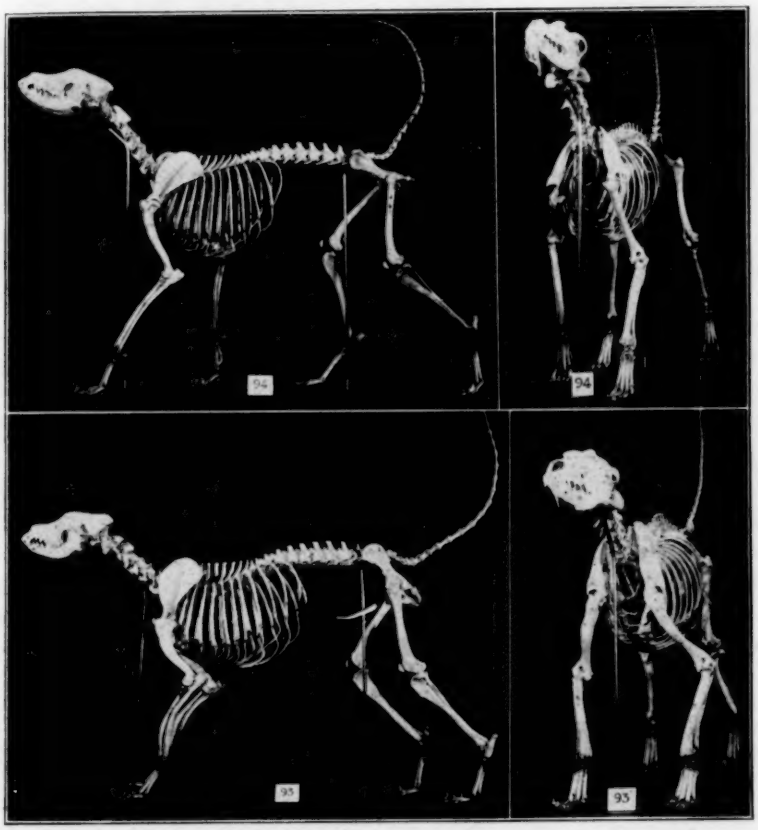

Fig. 3.—Figures 94 and 94 show a skeleton of a female fox-hound seen from lateral and front views. The leg bones are straight and slender. The appearance of this dog in life is shown in figure 2 *B*. Figures 93 and 93 show the skeleton of a male fox-hound from lateral and front views, showing rickets of the bones of the extremities. The bones are bent and thick and the position and shape of the legs are deformed. Figure 1 *B* shows the living appearance of the dog from which this skeleton was prepared.

1. Hess, A. F.: Difference in Calcium Level of the Blood Between Male and Female Cod, Proc. Soc. Exper. Biol. & Med. **25**:349, 1928.

I have been unable to find statistics giving the ratio of rickets in male as compared with female children. However, there may be also a sex difference here as there seems to be in cases of infantile tetany, which is more commonly shown by boys than girls as pointed out in the recent study by H. Bakwin and R. M. Bakwin.[2]

The strong contrast in bone form and general shape between the male and female members of this one litter of fox-hounds is shown in figure 3. The skeleton of a female (fig. 3, 94 and 94), is slender and straight boned and the bone is dense and hard. The skeleton of her brother (fig. 3, 93 and 93), has bent forearm bones with increased diameter, and these bones are poor and granular.

The living animals (figs. 1 and 2) show a clear-cut superiority of form in the extremities and general skeletal development in the sisters as contrasted with the brothers.

Nonidez [3] has been studying rickets in fowls for the past few years, and in a paper on the bones in avian rickets, he calls attention to the fact that the rachitic character appears earlier in the males. This, he suggests, may be due to the fact that the males grow faster and attain a heavier body weight when adult than do the females. Such an explanation would be suggested on account of the marked sexual dimorphism in fowls, the rooster being much larger and heavier than the hen. Among fox-hounds, however, there is slight difference in size between the sexes and their growth rates are closely the same. Thus it seems possible that there is an actual constitutional difference in calcium metabolism and bone formation between the male and female dog. If this is the case, a similar difference between the sexes possibly exists among other mammals as well.

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2. Bakwin, H., and Bakwin, R. M.: Serum Variation in Calcium Content of Infants' Serum, Am. J. Dis. Child. **34**:994 (Dec.) 1927.

3. Nonidez, J. F.: Studies on the Bones in Avian Rickets, Am. J. Path., in press, 1928.

PYURIA IN CHILDREN

THE USE OF THE CYSTOGRAM *

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In children, pyuria of long duration is associated frequently with organic changes and congenital anomalies in the kidneys, ureters, bladder or urethra. Such an organic basis for the development of pyuria has been pointed out in several series of cases, notably those of Beer,[1] Hyman,[2] Lowsley and Butterfield,[3] Smith,[4] Mixter,[5] and Helmholz.[6] The final diagnosis has usually rested on urologic investigation by means of the cystoscope. Direct examination is thus made of the urethra and bladder; and roentgenograms of the ureters and pelves of the kidneys are made following ureteral catheterization. But such instrumental examination is not without danger. Many children are not in a condition to undergo the trauma of cystoscopy with its not infrequent reaction, nor are they even suitable patients for general anesthesia, a necessary part of the urologic examination of young children. The difficulty of the procedure and the frequency of reactions are especially disturbing in infants.

Bumpus,[7] in the discussion of a paper by Helmholz, expressed the urologist's point of view, warning of the dangers of cystoscopy in children and strongly advising against it until a thorough examination of the patient had been made, and until the child had failed to respond to the usual treatment. Mixter, expressing a similar attitude, suggests

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* Received for publication, April 11, 1928.

* From the Infants and Children's Hospital and the Department of Pediatrics, Harvard Medical School.

1. Beer, Edwin: The Importance of the Recognition of Surgical Diseases in the Urinary Organs of Children, Internat. Clin. **3**:272, 1923.

2. Hyman, Abraham: Surgical Diseases of the Urinary Tract in Children with Special Reference to the Value of Cystoscopy, Am. J. Dis. Child. **15**:116 (Feb.) 1918.

3. Lowsley, O. S., and Butterfield, P. M.: Urologic Conditions Among Children, J. Urol. **16**:415 (Dec.) 1926.

4. Smith, R. M.: Roentgen-Ray Examinations in Diseases of the Kidney, Am. J. Dis. Child. **28**:678 (Dec.) 1924.

5. Mixter, C. G.: Surgical Aspects of Pyuria in Childhood, Boston M. & S. J. **195**:615 (Sept. 23) 1926; Urinary Obstructions in Childhood, Ann. Surg. **84**: 533 (Oct.) 1926.

6. Helmholz, H. F.: Congenital Abnormalities of the Urinary Tract in Childhood, J. A. M. A. **89**:1932 (Dec. 3) 1927.

7. Bumpus, in discussion on Helmholz: Congenital Abnormalities of the Urinary Tract in Childhood, J. A. M. A. **89**:1935 (Dec. 3) 1927.

that the child with pyelitis should be under observation six months or more before instrumental investigation is made. In the opinions of both the urologist and the pediatrician, cystoscopy to determine whether anomalies or organic changes are causing pyuria, is made only after a relatively long period of observation and treatment. And in this period the patient is studied most carefully by a series of procedures advocated also by the pediatrician and the urologist. Such procedures include a careful physical examination of the patient; chemical, microscopic and bacteriologic examination of catheterized specimens of urine, the determination of the residual urine, examination of the excretion of phenolsulphonphthalein and of the nonprotein nitrogen of the blood and the making of roentgenograms of the abdomen.

After such an investigation, the desire to acquire additional information constantly urges the shortening or omission of a period of therapy. But bearing in mind the dangers of cystoscopy one is led to consider other diagnostic methods, procedures which can be carried out with less discomfort and risk to the patient, and which may yield information either justifying the immediate use of the cystoscope or making its use unnecessary.

Cystography is such an additional procedure and one which frequently yields information of value. Hyman [2] recommended cystography if cystoscopy could not be performed or was contraindicated. Mixter [5] advised cystograms before cystoscopy, stating that they would demonstrate certain types of obstruction, ureteral reflux or irregularities of contour of the bladder. For a number of years the cystogram has been used in selected cases in this clinic, but only recently have my co-workers and I been impressed with the value of the method as a part of the routine examination of patients with pyuria. Experience with a relatively large series of cases has shown that cystography is most useful: (1) in demonstrating abnormalities of the bladder and ureters, often making cystoscopy unnecessary; (2) in determining the desirability of immediate examination with the cystoscope; (3) as an adjunct in patients in whom cystoscopic treatment would be inadvisable; and (4) in demonstrating the possibility of therapy by lavage.

TECHNIC

A sterile 12.5 per cent solution of potassium iodide is injected into the bladder through a catheter of as large size as can be passed through the urethra without undue discomfort to the patient. If a smaller catheter is used, the child can easily void around it and even force it out with the urinary stream. Any residual urine is withdrawn, and the solution of potassium iodide is injected from a large syringe. The pressure is increased slowly to avoid reflex contraction of an overstimulated bladder. The discomfort of the patient is carefully observed and used as an index to the amount of pressure to be exerted. When the child begins to manifest discomfort, the catheter is clamped off and the roentgenograms are taken

immediately. A syringe of sufficient capacity to hold the entire quantity of fluid to be injected shortens the time of the procedure, and makes possible a convenient temporary reduction of pressure while the position of the child is being changed for lateral views. When the roentgenograms have been taken, the potassium iodide solution is withdrawn, and the bladder is irrigated with boric acid solution. With this procedure there have been no reactions. If the subsequent irrigation is omitted, discomfort and frequency of urination may persist for several hours. The complete procedure is carried out on the roentgen-ray table. It requires little time and is without danger if the precautions regarding the discomfort of the patient are observed.[8]

In the normal child the cystogram shows only the outline of a well filled bladder. There is no irregularity of contour of the bladder, and no passage of iodide solution into the ureters.[9] But approximately 20 per cent of the children with pyuria of long-standing show reflux of iodide solution into the ureters. Sometimes reflux is the only abnormality noted. More often the ureter is dilated, and the pelvis of the kidney is clearly outlined. If only one ureter is filled, the infection is found to be most marked on that side, or limited to it. Considerable reflux with marked dilatation of the ureter indicates the possibility of therapy by lavage. This was done in one or two cases with apparent benefit to the patient.

REPORT OF CASES

CASE 1.—P. M., a girl, aged 5 months, born prematurely, had suffered from fever and malnutrition since the age of 2 months. On examination, the urine was found to contain pus.

A cystogram was made (fig. 1) which showed reflux into both ureters. The pelves of the kidneys were clearly outlined, but evidenced no abnormality. A ureteral kink was present on the right side. Such kinks have been suggested as causes for pus and albumin in the urine, but the bilateral reflux in this case indicated that this was not a factor.

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8. When the discomfort of the patient cannot be used as a guide to the amount of pressure exerted, the fluid is allowed to flow in under slight hydrostatic pressure. Elevation of the pelvis through the use of a tilting table is then of some advantage.

9. The anatomic structure which prevents backflow of the urine from the bladder into the ureter in the normal animal has been investigated by Satani (Am. J. Physiol. **49**:474 (Aug.) 1919; ibid. **50**:342 (Dec.) 1919) and more recently by Gruber (Proc. Soc. Exper. Biol. & Med. **25**:329 (Feb.) 1928.

The intravesical portion of the ureter appears to serve as a true valve and is capable of withstanding any pressure. In fact, pressure may be exerted in the bladder sufficient to rupture the organ without increasing the intra-ureteral pressure.

Excision of the intravesical ureter leads to hydro-ureter and hydronephrosis. The cause of the failure of the action of the valve in cases of pyuria is not clear. One cannot say whether the failure of the action of the valve occurs first and infection follows, or whether the infection precedes the failure of action. The history of the fifth case reported suggests that in tuberculosis, at least, the reflux may be secondary to the disease.

CASE 2.—M. M., a girl, aged 9 months, was brought to the hospital after an illness of two months' duration, which was characterized by fever, vomiting and loss of weight. Pus had been found in the urine six weeks prior to entry, and the child had been under treatment for that length of time. She was an exceedingly ill, malnourished, dehydrated infant. There was a large mass palpable in the right side of the abdomen. The urine contained extraordinary amounts of pus; fully one third of each specimen was pus sediment. A cystogram was made (fig. 2) which showed a dilated double ureter on the right side. A ureter was not visible on the left side. From the cystogram one could not say whether a left

Fig. 1 (case 1).—Cystogram showing a normal bladder with abnormal reflux into both ureters. The outlines of the ureters and pelves are normal except for the kink in the right ureter, which was thought to have no bearing on the infection in this case. These roentgenograms were reproduced through the courtesy of Dr. E. C. Vogt, roentgenologist of the Children's Hospital of Boston.

kidney was present, but the excretion of phenolsulphonphthalein of 25 per cent in two hours, and the fact that sometimes the urine voided was clear, made it seem probable that there was a left kidney. Dr. Mixter refused cystoscopy, owing to the critical condition of the patient. A right nephrectomy was done, a large pyonephrotic kidney being removed. The child made an uninterrupted convalescence following the operation. This case is of interest because of the

remarkable ease of demonstrating the malformation, and also because of its bearing on the problem of reflux in the normal ureter and kidney. Here the right ureters filled rapidly and easily, but there was no reflux into the left.

CASE 3.—J. T., a boy, aged 3½ years, was admitted to the hospital because of pyuria of two and a half months' duration. The illness began acutely, with fever, vomiting and dysuria. On numerous examinations the urine had shown large amounts of pus and a trace of albumin. Treatment over a period of two months

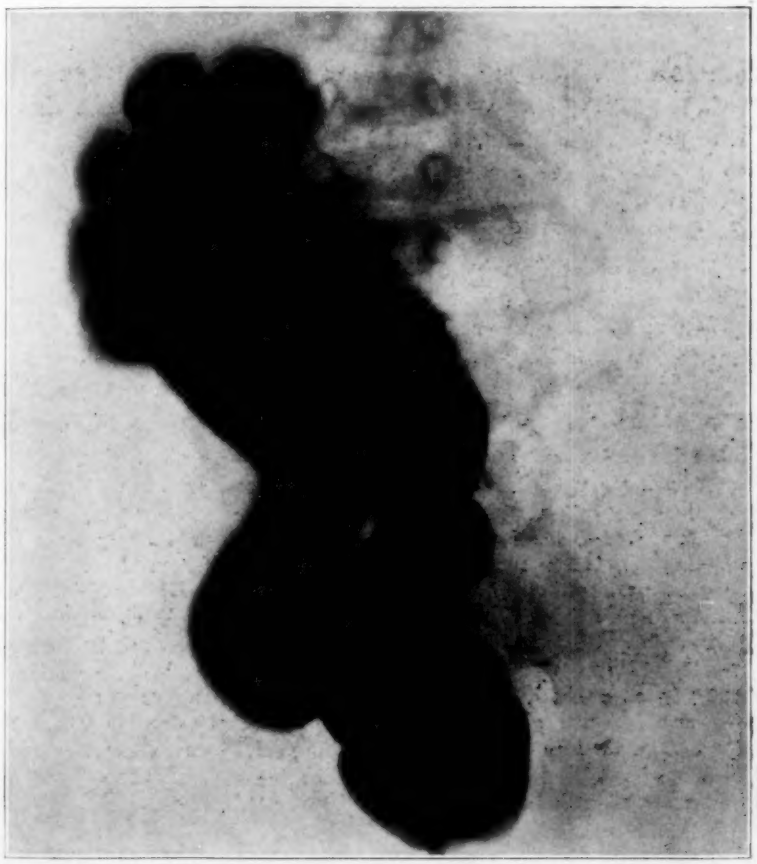

Fig. 2 (case 2).—Cystogram showing an extremely dilated double ureter on the right side. The double ureter with a pyonephrosis was thought to be the underlying cause of the infection. This was substantiated at operation.

was without benefit. A cystogram (fig. 3) was made revealing a normal bladder, but with reflux of iodide up the ureters into the pelvis of each kidney. The urologist subsequently refused to make a cystoscopic examination, feeling that the cystogram had shown all that could be expected from cystoscopy.

CASE 4.—L. N., a girl, aged 9, was admitted to the hospital following a febrile illness of one year's duration. Pus had been found in the urine six weeks before

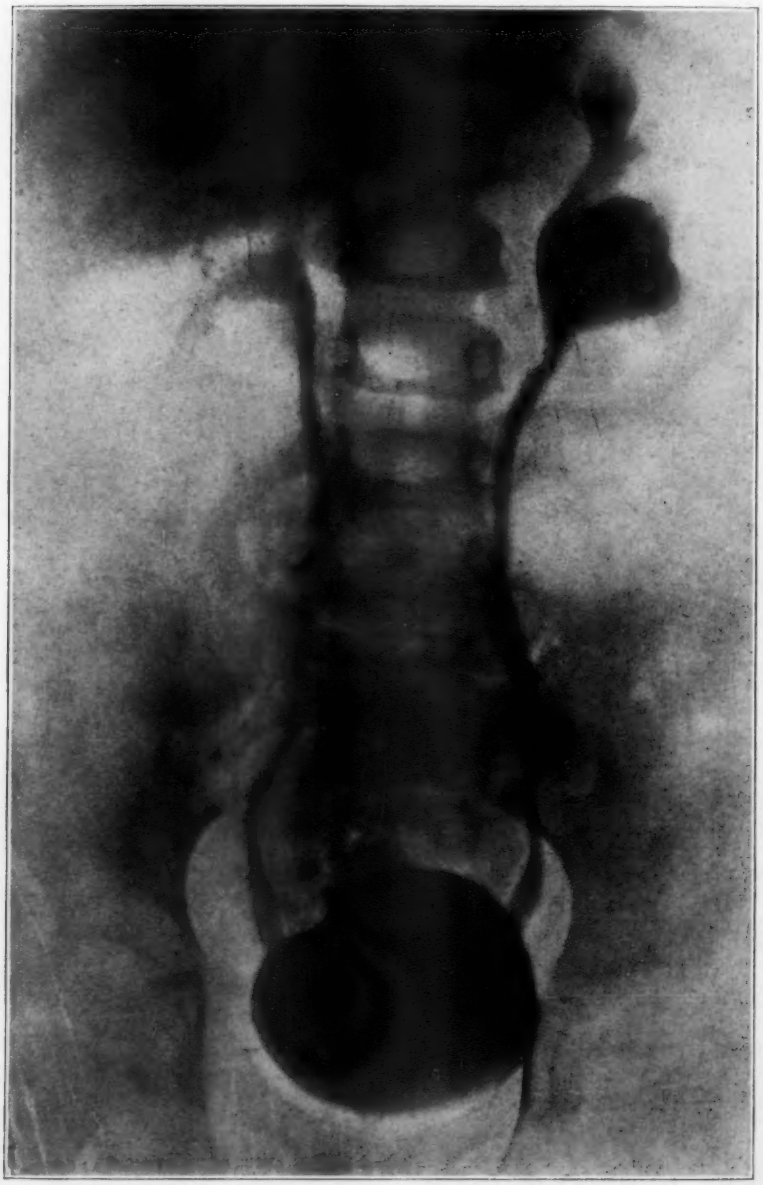

Fig. 3 (case 3).—Cystogram showing reflux into both ureters. The picture shows all that could reasonably be expected from pyelograms following cystoscopy.

Fig. 4 (case 4).—Cystogram showing reflux with dilation of the left ureter. Physical examination had previously shown tenderness in the region of the left kidney.

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entry. On physical examination the child had definite tenderness in the left costovertebral angle.

A cystogram (fig. 4) revealed a considerably dilated left ureter, confirming the greater involvement of the left kidney as suggested by physical examination. Cystoscopy with ureteral catheterization did not yield additional information.

CASE 5.—C. D., a girl, aged 7 years, had been losing weight for three months and had been disturbed by frequency of urination and enuresis. For six weeks she had complained of pain in the left side of the abdomen. Pus had been found in the urine on several examinations. Physical examination showed an under-

Fig. 5 (case 5).—Cystogram showing a contracted bladder and partial reflux into the left ureter. Subsequently, the lesions in the bladder and in the left kidney were proved to be tuberculous.

nourished girl, with a large and easily palpable left kidney. Intradermal tuberculin test (1:1,000) was strongly positive, and a roentgenogram of the lungs was suggestive of tuberculosis. The urine contained large amounts of pus but was repeatedly sterile on culture.

A cystogram (fig. 5) showed a small, irregularly shaped bladder which would hold only 50 cc. of the solution without causing marked distress. There was a reflux up the left ureter, and blood was obtained when the bladder was irrigated. This obviously was a case for more complete study. Cystoscopy revealed an

ulceration in a bladder too contracted to allow identification of the ureteral orifices. Inoculation of a guinea-pig with a catheterized specimen of urine resulted in the death of the pig from tuberculosis.

CASE 6.—The statement was made earlier that in about 20 per cent of the cases of chronic pyuria changes are shown by cystography. In many of the remainder one must have recourse to cystoscopy. The following is a report of such a case.

H. R., a girl, aged 5 years, had suffered for two years from attacks of abdominal pain associated with frequency and burning urination.

Physical examination did not show masses or reveal tenderness in the abdomen, but the urine contained a considerable amount of pus.

A cystogram showed only a well filled, apparently normal bladder.

Subsequently cystoscopy showed a stricture of the right ureter at the ureterobladder orifice.

SUMMARY

Chronic pyuria in children is often associated with organic changes in the urinary tract, which in many cases can be detected by the simple cystogram without recourse to cystoscopy. Cystography can be done quickly and easily without anesthesia or danger of shock. The percentage of cases in which valuable information is obtained is sufficiently large to warrant adding this procedure to those used routinely in the investigation into the cause of pyuria in children.

HEMORRHAGE OF THE SUPRARENALS IN THE NEW-BORN INFANT

DIAGNOSIS AND THERAPY *

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The occurrence of destructive hemorrhages in the suprarenals of the new-born infant is well known and has been extensively discussed. It seems to be established that such hemorrhages are much more common at or shortly after birth than at any other stage of life. While they are rather rare in the adult and only slightly more frequent in childhood, they have been observed by Mattei [1] in the new-born infant 16 times in 90 autopsies, by Lesser [2] 9 times in 240 and by Magnus [3] 8 times in 124 autopsies. Hamill [4] collected eighty-seven cases from the literature and added three more to the list. Most of these cases concern stillborn infants or infants who died shortly after birth in whom the diagnosis of suprarenal hemorrhage was not and could not be made. In the later period of early childhood, the clinical syndrome is more amenable to observation and diagnosis; recently such cases have actually been recognized in vivo (Rabinowitz [5]). In the new-born, an intra vitam diagnosis was made only once before. Corcoran and Strauss [6] reported a case of intestinal obstruction which developed five days after birth; operation revealed the presence of a large hematoma of the left suprarenal which produced complete occlusion of the colon.

We herewith report two cases in which intra vitam diagnoses of hemorrhage of the suprarenals were made.

REPORT OF CASES

CASE 1.—S., a male infant, whose mother was a multipara, was born at the anticipated term, and the delivery was normal and spontaneous. The mother was in labor about four hours. The infant weighed 7 pounds and 2 ounces (3.2 Kg.).

* Received for publication, March 17, 1928.

* From the Department of Laboratories and the Pediatric Department, United Israel Zion Hospital.

1. Mattei: Sperimentale **2**:3, 1863.
2. Lesser: Atlas d. gerichtlichen Medizin, Hirschwald, Breslau, 1883.
3. Magnus: Berl. klin. Wchnschr. **48**:1119, 1911.
4. Hamill: Arch. f. Pediat. **18**:81, 1911.
5. Rabinowitz: Am. J. M. Sc. **166**:513, 1923.
6. Corcoran, W. J., and Strauss, A. A.: Suprarenal Hemorrhage in New-Born, J. A. M. A. **82**:626 (Feb. 23) 1924.

He cried spontaneously, and there was no evidence of asphyxia. Twelve hours after delivery, the temperature suddenly rose to 106 F. and the respiration became extremely rapid, ranging between 120 to 130 per minute. The alae nasi dilated with each inspiration, and a yellowish pallor was present. Because of the respiratory embarrassment and the elevation of temperature, a diagnosis of pneumonia appeared logical in spite of the absence of definite physical symptoms. These symptoms persisted until the following morning, when the infant was seen by us.

Examination.—Examination revealed a critically ill infant. In addition to the yellow pallor, the lips and finger-tips were cyanotic. The respiration was extremely rapid, 130 per minute. There was a definite expiratory grunt. Results of examination of the heart and lungs were negative. Hemorrhages into the skin or mucous membranes were not present and tumor masses were not palpable in the abdomen. A diagnosis of suprarenal hemorrhage with acute suprarenal insufficiency was made. The temperature remained elevated during the entire day, and the symptoms and signs already described became more intense. The infant died the same day at 11:45 p. m.

Fig. 1.—Hemorrhagic infarction of the right suprarenal. The suprarenal is in its normal position above the kidney.

Autopsy Observations.—There were no symptoms of pneumonia, both lungs containing air throughout. There were a few petechiae the size of a pinpoint beneath the pulmonary pleura and the pericardium. Slightly larger petechiae were found scattered over the mucosa of the small intestines. Except for the suprarenals, autopsy observations were otherwise negative. Both of the suprarenals were considerably enlarged, their size equaling that of the kidneys (fig. 1). Their shape was well maintained, and they were found at their usual location. Their color, however, was a dark bluish red, and they were firm to touch. On section, very little suprarenal structure could be seen, the whole organ being diffusely infiltrated with blood. Only around one of the edges of the left suprarenal was any tissue left which could be identified as suprarenal cortex. Cortical tissue did not remain in the other suprarenal. Histologic examination of the suprarenals revealed the picture of hemorrhagic infarction. No medullary cells were seen; the

small amount of cortical tissue which was still present stained poorly with hematoxylin-eosin. In the liver, a large number of scattered foci of necrosis could be seen; they were irregular in distribution.

CASE 2.—F. W., a female infant, was delivered on Nov. 15, 1927, by Dr. Mohr at the United Israel Zion Hospital. This was the mother's first pregnancy; the labor was difficult and lasted about forty-eight hours. The early stage of labor was normal until complete dilatation of the cervix uteri occurred, which lasted twelve hours; the head was then arrested at the outlet by a funnel pelvis. After thirty-six hours, the fetal heart became rapid, meconium was passed, and labor was terminated by the application of low forceps. At birth, the infant cried spontaneously and vigorously. The color was good; the weight was 7 pounds and 6 ounces (3.2 Kg.) . Twenty-four hours after delivery, there was an elevation of temperature to 100 F.; forty-eight hours after delivery, the temperature was 102 F., and seventy-two hours after delivery, 103 F. At this time notes on the chart recorded that the infant's general condition was poor, the color of the skin was yellowish gray and cyanosis was present. Small hemorrhages were observed in the sclera of the right eye and in the mucous membranes of the hard palate. The anterior fontanel was small and did not bulge. Convulsions or twitchings were not observed. The bleeding time was eight minutes, the coagulating time was four minutes; the platelet count was 240,000. Sixty cubic centimeters of whole blood was given intragluteally. On the morning of November 19, the condition of the infant was somewhat improved. The temperature had dropped to 101.6 F., and the cry was more lusty. An edematous area over the right buttocks, where the blood had been injected, was noticed. On the afternoon of the same day, cyanosis was still present and generalized twitchings appeared for the first time. At this time, one of us was asked to see the infant. Physical examination revealed an infant whose general condition was poor, presenting the clinical picture of a condition diagnosed as sepsis neonatorum. A yellowish pallor was observed. Respiration was rapid and shallow. The fontanel was about 2 by 3 cm. and not bulging. The lips were pale but became cyanotic when the infant cried. There was a hemorrhagic area in the hard palate; vaginal bleeding was also present. A rounded, irregular mass, about the size of an orange, was felt in the right hypochondrium. Anteriorly the mass extended from the costal margin down to the brim of the pelvis, and posteriorly it extended into the right flank. The tumor was firm and movable, and it occupied the position of the right kidney. Otherwise, the results of the examination were negative. A diagnosis of hemorrhage into the right suprarenal was made. One cubic centimeter of the cortical hormone interrenin isolated by one of us[7] was injected intravenously at 8 p. m. of the same day. At the time of the injection, the respirations were 51 per minute. At 11:30 p. m., the respirations decreased to 31 per minute; 2 cc. of interrenin was again injected subcutaneously. On November 20, the condition of the infant seemed slightly improved. The temperature fluctuated between 99 and 100 F. The mass, however, had definitely increased in size, and the right flank was definitely fuller than the left. Two injections of 2 cc. each of interrenin were given subcutaneously at eight hour intervals. On the next day the infant appeared worse, although the cyanosis was not as marked as on the previous days. The cry was weak, and the infant refused practically all nourishment. Further vaginal bleeding was not observed. The mass had again increased in size, and the skin over

7. Goldzieher: Interrenin das Hormon der Nebennierenrinde, Klin. Wchnschr. **7**:980, 1928.

the abdomen was tense, shiny and definitely discolored, greenish blue, particularly in the flank. Two injections of 2 cc. each of interrenin were again given at eight hour intervals. On November 22, the infant showed some improvement. The color was somewhat better, although the temperature had again risen to 102 F. A definite cellulitis was observed over the left buttock and thigh, and hot boric acid compresses were applied. Profuse persistent vomiting was noted. Two injections of interrenin were again administered.

From November 23 to November 27, the temperature fluctuated between 101 F. and 105 F., and the respiration ranged from 60 to 30 a minute, depending on the injections of interrenin; in other words, half an hour after the subcutaneous injection of interrenin, the respirations dropped from 60 to 30; they remained at this level for from four to six hours and then gradually increased again. Vomiting was persistent during this time and hypodermoclyses of 10 per cent dextrose solution and a solution of sodium chloride were given. One cubic centimeter of interrenin was given subcutaneously during this time daily. The mass in the right flank, however, remained unchanged in size. Vaginal bleeding recurred on November 25. At this time an enlargement of the spleen was also noted for the first time. On November 28, vomiting had stopped and mother's milk, given every two hours in 30 cc. doses, was retained by the infant. On November 30, an abscess over the right trochanter was incised, and 1 ounce of pus was evacuated. From this time on the child continued to improve although the temperature fluctuated between 102 F. and 103 F. On December 7, hemoglobin estimation (Sahli) was 52 per cent. The red blood count was 2,500,000; the white blood count was 12,000; the differential count was: segmented polymorphonuclears, 42 per cent; staff forms, 3 per cent; lymphocytes, 38 per cent, and monocytes, 17 per cent. Roentgen-ray examination of the abdomen, made on December 7, did not reveal anything definite. On December 8, the infant received a transfusion of 40 cc. of whole blood intravenously. On December 10, the general condition of the infant was much improved; the color of the skin had changed from yellow to pink; vomiting had disappeared, and the tumor mass in the right side appeared decidedly smaller. On December 12, the infant was discharged from the hospital. The weight at this time was 7 pounds and 6 ounces (3.2 Kg.)—its birth weight. The lowest point in the weight curve was reached on the fifth day of the infant's life, when it dropped to 6 pounds and 4 ounces (2.7 Kg.). From that time until the child was discharged, a slow irregular gain was observed. The tumor mass in the right hypochondrium and right flank was still present and irregular in outline, but it did not reach below the level of the umbilicus. The infant was observed by Dr. Mohr following discharge from the hospital. He reported a regular and progressive decrease in the size of the tumor mass, and by January 3, the mass had completely disappeared. The infant made regular and rapid gains in weight, and by January 15, it presented the appearance of a normal infant.

In our first case, the diagnosis was confirmed by autopsy, but in our second case we have to depend on clinical evidence for substantiation of the diagnosis made. This may be summarized as follows: Clinical symptoms were identical with those in the first case: the appearance of a rapidly growing mass in the abdomen with subsequent discoloration of the adjacent soft tissue; gradual, slow disappearance of the mass as the infant recovered; immediate response to the administration of the cortical hormone; recovery as a result of continued hormone therapy.

COMMENT

Pathogenesis.—Hemorrhages of the suprarenals in adults or in older children are brought about by a thrombosis of the suprarenal veins, by bacterial infections or by the effect of toxins. In the new-born infant similar causes may operate occasionally; often, however, there is no evidence of either thrombosis or an infectious process. It is reasonable to assume, therefore, that bleeding is brought about by trauma and unusual susceptibility of the suprarenals to hemorrhage. The latter may be explained by the peculiar physiologic changes which the suprarenals undergo immediately after birth. The major part of the cortex, i. e., the reticularis and the trabecularis, is subject to rapid

Fig. 2.—Posterior view; the left suprarenal is intact; the right is transformed into a hemorrhagic mass; the right kidney is pushed downward by hemorrhagic infiltration of perirenal tissues. Note the size of the right suprarenal in comparison to the left suprarenal and kidney.

involution, which leaves only the exterior layers of the cortex intact. After the disappearance of the glandular cells of the cortex, the wide and thin-walled capillaries remain unsupported, showing in almost every new born infant a remarkable degree of congestion. Any trauma, either that of birth proper or any postnatal injury may cause rupture of these congested vessels. Sudden changes in blood pressure, such as are produced in the new-born infant by crying, vomiting, coughing, etc., may have similar results.

Studies made by one of us on the suprarenals of a large number of new-born infants and young children seem to indicate that the physiologic involution of the cortex may begin in utero shortly before birth

and may progress more or less rapidly immediately after birth. Hence we believe that the anatomic structure of the suprarenal cortex is the other factor which, together with the severity of the trauma, determines the occurrence and severity of a hemorrhage.

The hemorrhage may remain within the capsule of the suprarenal gland or may extend beyond its boundaries. In the former case, the suprarenal may be enlarged and solid, as in the first case we reported, or it may be transformed into a hemorrhagic cyst, as described by Lesser,[2] Dienst,[8] Hamill,[4] Gjorgewitsch[9] and others. If the capsule ruptures, the hemorrhage may infiltrate the retroperitoneal tissue, as it apparently did in the second case reported by us; we have also observed this repeatedly at autopsy. Several of these cases are in our collection (fig. 2), and similar observations are indicated by the majority of the cases reported. A much rarer complication is the bursting of the hematoma and subsequent bleeding into the peritoneal cavity. This has been seen by Ahlfeld[10] and Hamill[4] and in other cases quoted by Thomas.[11]

Symptoms.—It is obvious that the symptoms of suprarenal hemorrhage will vary according to the extent of the bleeding and the damage to the glandular parenchyma. In large hematomas, particularly in hemoperitoneum, the symptoms are primarily those of severe internal bleeding, rapid pulse, thirst, marked pallor, collapse, etc. Peritoneal irritation may add further complicating factors, such as vomiting, abdominal distention, intestinal obstruction. Vomiting, diarrhea, convulsions, elevation of temperature, dyspnea, cyanosis and hemorrhages into the skin and mucous membranes are the most constant symptoms observed. One case is reported by Corcoran and Strauss,[6] one by Gunson[12] and three by Langmead[13] in which fever was present. Tronconi,[14] however, reports a case in which hypothermia was encountered. Severe dyspnea was observed by Joseph and Rabau[15] in their case. Cyanosis was present in the cases reported by Tronconi and by Joseph and Rabau. Purpuric hemorrhages were found in three of Langmead's cases; Roessle[16] noted a patchy pigmentation of the palate in one case, and Tronconi observed hemorrhages into the skin in his

8. Dienst: Monatschr. f. Geburtsh. u. Gynäk. **19**:1, 1904.
9. Gjorgewitsch: I. D. Zurich, 1920. Ueber Blutcysten d. hemgevorenen, Speidel and Wunzel.
10. Ahlfeld: Arch. f. Hilk., 1870, p. 491.
11. Thomas: Handbuch der allgemeinen Pathologie des Kindes, Wiesbaden, Bergmann, 1913, vol. 2, p. 360.
12. Gunson: Proc. Roy. Soc. Med., vol. 54, 1914-1915.
13. Langmead: Lancet **71**:1496, 1904.
14. Tronconi: Pediatria **29**:266, 1921.
15. Joseph and Rabau: Zentralbl. f. Gynäk. **49**:48, 1925.
16. Roessle: München. med. Wchnschr. **57**:1380, 1910.

case. Vomiting and diarrhea were noted by Corcoran and Strauss, Tronconi, Toepffer [17] and Dörner.[18] Dörner also observed extreme restlessness in one case. Icterus occurred in a number of cases reported by Dörner, Tronconi, and Toepffer. Symptoms as a result of pressure of the hematoma on adjacent structures are seen at times. Thus, obstruction of the intestines as a result of occlusion of the colon occurred in a patient of Corcoran and Strauss, and icterus due to compression of the common bile duct was noted in a patient by Tronconi.

The two outstanding symptoms in both of the cases reported here were hyperpyrexia and dyspnea. In the first infant, the respiratory rate was even more rapid than that usually encountered in the severest cases of pneumonia (130 per minute); the excursions were shallow, and the heaving of the wall of the chest gave it an appearance not unlike that of a heart in flutter. In the second infant, the respiration was not nearly so rapid (60 per minute), yet the rate was entirely out of proportion to the elevation of temperature. It appears that the height of the temperature and the degree of dyspnea are in direct proportion to the amount of cortical tissue destroyed. For instance, in the first patient the cortex of both suprarenals was almost totally destroyed; while in the second, there was no clinical evidence of hemorrhage in the left suprarenal. Thus, the temperature rose to 106 F. in the first infant and fluctuated between 102 and 103 F. in the second. Cyanosis was observed in both patients, but convulsions occurred only in the second infant and were both clonic and tonic. The cellulitis of the thigh which complicated the second case was probably the result of a secondary infection at the site of the injection of the blood. It is interesting to note, however, that Gunson's patient,[12] in whom a large hemorrhage within the intact capsule of the right suprarenal gland was revealed at autopsy, also manifested a cellulitis of both forearms. Whether the occurrence of cellulitis was incidental in both cases or whether it is part of the symptomatology of suprarenal insufficiency in that a lowered resistance against infection results, it is difficult to state at this time. When the hemorrhage is extensive, the hematoma may be palpated through the abdominal wall; most often, however, a tumor mass cannot be felt.

If the hemorrhage is unilateral, the symptoms of acute suprarenal insufficiency may be entirely absent; they may set in, however, in spite of one suprarenal being intact. It is reasonable to explain these rare cases as being due to reflex inhibition of the glandular function, comparable to the reflex anuria of an intact kidney after acute injury of the other. Observations in Addison's disease confirm this assumption. If both or the major parts of both glands are destroyed, the symptoms

17. Toepffer: Arch. f. Gynäk. **112**:342, 1920.
18. Dörner: Vrtljschr. f. gerichtl. Med. **26**:272, 1903.

of cortical insufficiency will prevail over those of insufficiency of the medulla. In the new-born infant, the chromaffin tissue of the medulla is rather scanty, and its loss therefore is of little consequence. Moreover, it seems that in the embryo and in the new-born infant, the extra suprarenal chromaffin tissues (paraganglia) have a comparatively larger share in the function of the chromaffin system than they do later. The preponderance of the medulla over the paraganglions becomes more marked in later childhood and adolescence. Hence the symptoms of suprarenal destruction in the new-born infant are more likely to be of cortical origin; whereas, in later childhood or in adult life, the symptoms of chromaffin insufficiency are more in the foreground.

Diagnosis.—It is the consensus of opinion of various observers that the diagnosis of suprarenal hemorrhage in the new-born infant cannot be made intra vitam. Indeed, Tronconi said definitely that the diagnosis can be made only at autopsy. In the cases reported by Fourdinier,[19] Toepffer,[17] Lundsgaard,[20] and Dörner [18] the diagnosis was made only at autopsy. We believe, however, that in the presence of a fever of unknown origin and an increased respiratory rate which is out of proportion to the rise in temperature, together with negative chest observations, hemorrhage into the suprarenals should at least be suspected. The presence of a yellowish pallor with cyanosis of the lips and fingertips may be regarded as confirmatory evidence. If, in addition, a progressively increasing mass is felt in either flank with or without discoloration of the skin in that region, it is safe to make a definite diagnosis of suprarenal hemorrhage.

Treatment.—The two main activities which we may ascribe to the suprarenal cortex are the regulation of temperature and respiration. This is borne out by a multitude of recent physiologic investigations. Clinical observations of other authors also bear out this point (Dienst,[8] Corcoran and Strauss,[6] Joseph and Rabau [15]).

Guided by these considerations, we did not attempt to influence the course of the disease in our second case by the administration of epinephrine. Instead, we administered only the cortical hormone, interrenin, which did not fail to relieve the symptoms of the acute cortical insufficiency. Further explanation, however, seems necessary to account for the lasting effect of our therapy, which prevailed even after the injections of hormone were discontinued. We can offer the following suggestion: Parts of the left suprarenal or the whole of the left gland were probably uninjured and recovered from the shock or were relieved from reflex inhibition during the period in which life was maintained by means of hormone administration. It is also possible that there were

19. Fourdinier: J. d. sc. méd. de Lille **2**:272, 1912.

20. Lundsgaard: Virchows Arch. f. path. Anat. **210**:164, 1912.

extra suprarenal foci of cortical tissue, so-called aberrant interrenal glands, either in the vicinity of the suprarenal or elsewhere in the abdomen. The respite given by the hormone therapy might have been utilized by these tissues for compensatory hypertrophy, such as can be seen after operative removal of the main glands in rodents.

Spontaneous recovery after suprarenal hemorrhage is not impossible, but apparently this happens only if the injury is of minor severity. Several cases are reported in the literature in which incidental changes were found in the suprarenals which were interpreted as signs of old hemorrhages (Karakascheff,[21] Simmonds,[22] Goldmann,[23] Gierke[24]); they involved parts of the medulla and the reticularis of the cortex. Scars in the center of the suprarenal with hemosiderin deposits, calcification and even bone formation have been seen repeatedly by us. The limited extent of these lesions, however, proved to our mind that the original hematoma could not have been of major size and importance. We do believe, therefore, that our second patient could not have recovered from the apparently extensive lesions without the aid of the injections of the hormone.

Our two cases seem to bear out the following conclusions:

Suprarenal hemorrhage in the new-born infant can be diagnosed from its symptoms, such as sudden onset of high temperature and rapid breathing, and occasionally by the presence of a palpable tumor in the abdomen, or by punctiform purpuric hemorrhages of the skin or mucous membranes. Exsanguination or intestinal obstruction may justify surgical intervention; otherwise, patients with the symptoms of acute cortical insufficiency should be treated by continued administration of the cortical hormone.

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21. Karakascheff: Beitr. z. path. Anat. u. z. allg. Pathol. **36**:401, 1904.
22. Simmonds: Virchows Arch. f. path. Anat. **170**:242, 1902.
23. Goldmann, I. D.: Ueber Nebennierenblutungen bei Neugeborenen, Kiel, Fenke, 1908.
24. Gierke: Beitr. z. path. Anat. u. z. allg. Pathol., Festschrift f. Arnold, 1905.

Case Reports

PTERYGIUM COLLI CONGENITUM (CONGENITAL WEBBING) *

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In 1883, Kobylinski [1] described a remarkable deformity of the skin of the neck in a young man suffering from pulmonary tuberculosis. On both sides of the neck there was a pronounced fold of skin running from the mastoid to the acromion. Each fold was prominently visible when the head was turned in the opposite direction, the shoulders being shrugged. In the performance of this action while the patient was recumbent, a cavity was formed which would hold not less than 45 cc. of water. The mobility of the head was not seriously impaired.

The following is the report of a case of an infant, aged 6 weeks, who showed the same symptoms.

REPORT OF CASE

Frans A., born on July 2, 1927, was admitted to the children's ward of the "Binnengasthuis" in Amsterdam on August 6, suffering from congenital vitium cordis and bronchitis. Further examination brought the following abnormalities to light: At first sight, the neck gave the impression of being too short, and the skin formed wide, curtain-like folds on both sides, from the top of the mastoid to the acromion (figs. 1 and 2). Closer examination proved that a real shortening of the neck did not exist, but that this illusion was occasioned by the folds, which in their turn proved to be due, not to a superfluity, but rather to a deficiency, of the skin in this region. This was easily demonstrated by the excessive shortness of the skin on either side of the neck when the head was inclined toward the opposite shoulder. When the head was bent backward, the entire skin of the throat as far as approximately 2 cm. from the median line was similarly stretched (fig. 3). This conclusively proved that the curtain-like folds were caused because the skin was too short to stretch perpendicularly downward from the mastoid to the clavicle and laterally from this point to the acromion. It was thus forced to bridge over the distance between the acromion and the mastoid in a direct line. When not stretched, the folds of the neck were loose and felt soft, no difference from normal skin tissue being noticeable.

Results of roentgen-ray examination of the cervical and thoracic spine were negative. Neither synostosis nor absence of any vertebrae was apparent. Antecedents with this or any other deformities were not traced in the family. Two months after admission, the child was discharged considerably improved in health.

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* From the Department of Pediatrics, University of Amsterdam

1. Kobylinski, O.: Ueber eine flughautaehnliche Ausbreitung am Halse, Arch. f. Anthrop. **14**:343, 1883.

Fig. 1.—Pterygium colli congenitum (anterior view).

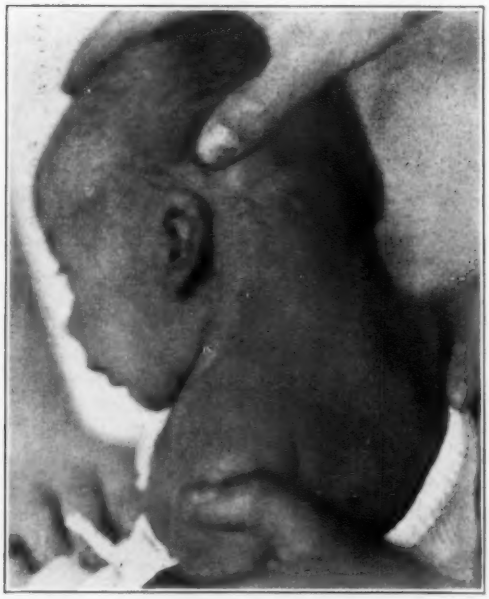

Fig. 2.—Pterygium colli congenitum (side view).

Cases of pterygium colli congenitum are rare, Kobylinski having been the first to describe the abnormality under discussion. A second case was reported by Bussière [2] in 1902; the patient in this case was a Hindu child, aged 12 years. In the latter case, as in that of Kobylinski, the mobility of the head was not impeded to a marked degree. The fold on the right side of the neck was more developed than that on the left. In this case, as in the case of Frans A., other abnormalities were present; namely, deformities in the bones and joints.

The third case was described in 1902 by Funke.[3] His patient was a girl, aged 15. Here, again, the movement of the head was unimpaired. The fold, densely covered with hair, projected 3 cm. beyond the normal neckline; it was soft and slid loosely over the subcutaneous tissue. Accompanying symptoms reported were considerable retardation of

Fig. 3.—Pterygium colli congenitum (anterior view).

sexual development, absence of breasts and nipples and total lack of hair in the axillae and mons veneris. Menstruation had not yet begun.

In 1925, Frawley [4] described four cases, in two of which a pronounced restriction of movements of the head existed. The head was sunken between hunched shoulders and could not be turned in any direction independent of motion of the shoulders. These two patients may thus be regarded as having real short necks.

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2. Bussière, J. A.: L'homme au cou de capelle, développement anormal d'un faisceau musculaire acromio-mastoidien rudimentaire, malformation congénitale rare, observé à Pondichéry (Indes Orientales), Ann. d'hyg. et de méd. colon. **5**:686, 1902; quoted by Frawley: Congenital Webbing, Am. J. Dis. Child. **29**: 799 (April) 1925.

3. Funke: Pterygium colli, Deutsche Ztschr. f. Chir. **63**:162, 1902.

4. Frawley, John M.: Congenital Webbing, Am. J. Dis. Child. **29**:799 (June) 1925.

Roentgen-ray examination here was unsatisfactory, the short neck occasioning difficulty in counting the cervical vertebrae, two of which seemed to be missing.

When one takes these facts (real shortness of the neck, limitation of mobility of the head, absence of satisfactory roentgen-ray proof) into consideration, these cases should not be classified with those of the congenital deformity under discussion.

The third of the four cases reported by Frawley occurred in a woman, aged 28. The neck was of normal length. Roentgen-ray examination of the cervical spine showed rudimentary cervical ribs, but was otherwise unimportant.

The fourth and last case, that of a girl, aged 7, was only briefly mentioned; reference was not made to the length of the neck, mobility of the head or roentgen-ray examination.

In order to get a better insight into the nature and origin of this deformity, it is necessary first to discuss another anomalous condition—real shortness of neck—the congenital abnormality described in extenso for the first time by Klippel and Feil [5] in 1912 and called, as a rule, by the names of these two authors, Klippel-Feil's disease. Here, some cervical vertebrae are grown together, sometimes even one or more thoracic ones; hence the names, thorax cervicalis and "hommes sans cou." A marked limitation of the mobility of the head is characteristic of this deformity, and sometimes accompanies the skin folds already described. However, a fundamental distinction must be made between these two.

The folds of the skin which are sometimes found in persons with Klippel-Feil's disease must be considered from the same standpoint as that other much more important abnormality, the deformity in the cervical spine. Klippel-Feil's syndrome, whether it is accompanied by folds of skin or not, may be easily distinguished clinically from pterygium colli (the name as first given by Funke). For the last diagnosis, the following characteristic features must be present: (1) The mobility of the head is affected only slightly or not at all. (2) There is often an illusive but never a real shortening of the neck. (3) The results of the roentgen-ray examination are always negative; i. e., neither a growing together nor an absence of the vertebrae is found. In the majority of cases of pterygium colli reported up to the present time, other congenital abnormalities were also encountered.

With regard to the origin of the malformation here described, the following facts are of some importance: Kobylinski assumed that a variation of the musculus trapezius (insertion as far as into the mastoid)

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5. Klippel, M., and Feil, André: Un cas d'absence des vertèbres cervicales avec cage thoracique remontant jusqu'à la base du crane (cage thoracique cervicale), Nouv. iconog. de la Salpêtrière **25**:233, 1912, quoted by Frawley.

or the musculus splenius capitis et colli comes into play. As he saw similar folds of skin in the picture of a chimpanzee, he considered the possibility of an atavistic feature.

Funke removed the folds. At this operation, he found the trapezius in the lower and posterior part of the fold, and the sternocleidomastoid in the upper part. Furthermore, it looked as if the skin of the neck had been grasped on either side by a hand which had lifted it up and kept it in that position during fetal and postembryonal growth. A permanent extension would thus have been exercised on the auricle as well as on the lateral portions of the skull. According to Funke, amniotic adhesions during fetal life (perhaps due to inflammation) are the cause of this traction and may thus explain the origin of pterygium colli. This hypothesis was based on other malformations also found on the head of the patient. The auricle and the auditory canal were drawn downward and backward, so that the drum could not be seen. The palate was highly arched. Pars horizontalis ossis palatini and processus alveolaris maxillae also had a downward and backward tendency.

L. Bolk, professor of anatomy at the University of Amsterdam, when shown the photographs of the patient described in Frawley's article, expressed the opinion that it seemed to him improbable that a lack of one or two vertebrae should be the cause of the folds of skin as this lack is rare, only two cases having been described.

In the present case of pterygium colli, roentgen-ray examination showed the vertebral column to be entirely normal. Moreover, it must be borne in mind that an abnormal condition of the vertebral column need not of itself cause a lack of skin in the region of the neck, so that the cause is more likely to be ascribed to a primary change in the soft parts themselves. It is evident that the folds of skin may be accounted for either by a variation in the direction of the muscles or by a primary malformation of the skin. The latter is, *a priori*, improbable, as it is recognized that the skin, to a great extent, accommodates itself to the topographic conditions of the underlying tissue as well as to the changes in its own surface. One could hardly assume that in this case this power of accommodation should have been absent, with a consequent permanent shortening of the neck. On the contrary, it is probable that a variation in the shape or direction of one or more muscles should be considered as the cause of these folds of skin. Two possibilities remain: 1. One or more of the long muscles in the region of the cervical vertebral column may have taken an abnormal direction. 2. There may have been a variation in the platysma, the skin muscle; this muscle must be considered a rudiment of the panniculus carnosis as found in horses.

On being shown the photographs of Frawley's patient, Professor Bolk ascribed the cause of the malformation to a variation of the

platysma myoides. This seems the most likely, on account of the softness of the folds and their great mobility in relation to the underlying tissue.

The argument against this conclusion is that the platysma under normal conditions is partially inserted into the lower edge of the mandible, while the posterior fibers sweep over the angle of the mandible, become continuous with the musculus risorius and are inserted into the fascia parotideomasseterica. Hence its most lateral fibers are always found in front of the ear, so that in any case they could not form a fold located between the acromion and mastoid. Nevertheless, this argument is not of great importance, as variations in both size and direction of the platysma are of frequent occurrence.[6] Insertions into the os occipitale, processus mastoideus and musculus auricularis posterior, which are all behind the ear, are frequently described (Zagorski, Henle). In short, it is probable that this malformation must be ascribed to an abnormal extension of the platysma.

In the case reported, postmortem examination gave an opportunity to get a better insight into this matter.

Two weeks after being discharged from the hospital, the patient was taken to the Emma Children's Hospital suffering from a serious inflammation of the lungs, to which he succumbed the following day.

Dr. J. C. Schippers, director of this hospital, kindly invited me to assist at the necropsy, which he himself performed. In relation to the cases here described, only the following results are of interest:

REPORT OF NECROPSY

The folds of skin were clearly visible. If the head was bent to one side, the fold on the other side was stretched. The skin of the neck, as far as approximately 2 cm. from the median line, was also stretched but to a less degree than the fold at the side. The neck was not too short; seen from the back, it appeared broad, the shoulders extending only a little beyond it. The hair margin was normal.

An incision was made from the center of the chin approximately half way down the sternum. From here, a second incision was made horizontally to the right around to the left shoulder-blade. The portion of skin detached in this manner and the underlying layer of fat were removed as far as the skull.

Under the uppermost fourth of the fold of skin, the upper part of the musculus sternocleidomastoideus was found; under the lowest fourth, a small part of the lateral margin of the musculus trapezius. This corresponded exactly with Funke's report.

It was certain, however, that neither of these muscles could be the real cause of the fold, as they both soon took another direction. Moreover, they were found lying deep under the skin, and therefore the possibility was ruled out that, by raising the skin at the acromion and the mastoid, they had caused the fold.

After removal of the skin, topographic abnormalities were not exposed, and it must be emphasized that variations in the direction and insertion of the long muscles of the neck were not found.

6. Le Testut: Les anomalies musculaires chez l'homme, Paris, 1884. Le Double: variations du système musculaire de l'homme, Paris, 1896.

Once the fold of skin was loose from the underlying tissue, it retracted strongly in a vertical direction. When the skin was replaced over the underlying tissue, the shoulder and neck assumed a normal outline, but considerable deficiency of skin was manifested, leaving a considerable portion between the musculus pectoralis and musculus deltoideus uncovered (fig. 4). When smoothly spread out, the skin itself did not bear any further trace of the folds. Furthermore, it was evident that the fold was not only formed by the skin, but that the fascia colli superficialis was also involved.

Just inside the fold of skin, following its direction closely, a cordlike structure appeared, better visible after removal of the skin. At the right side of the neck,

Fig. 4.—Pterygium colli congenitum at postmortem examination. The lack of skin is clearly visible.

where the skin was still unimpaired, a similar cord might be felt on palpation. This cord proved to be a fold of the fascia colli superficialis, as it disappeared when the fascia was stretched in a horizontal direction.

At the right side, two little pieces of the fold were removed for microscopic examination, great care being taken to excise only skin and underlying tissue but no muscle. One piece was removed from about the middle of the fold; the other, from a little behind the insertion of the musculus sternocleidomastoideus at the processus mastoideus at the end of the fold.

The following may serve as a confirmation of the hypothesis that a lack, not a superfluity, of skin was the cause of webbing of the neck: The little pieces of skin, when removed, left such gaping wounds as to make it appear as though two

vertical, not two horizontal, incisions had been made. Both wounds were stitched in a vertical direction, with a resultant normal neckline at this side.

Some importance may also be attached to the following additional details of the necropsy: The heart was contracted, and the apex was formed by the left ventricle. Its length was 72 mm., its width, 40 mm. Both atria were overfilled with blood. The wall of the left ventricle was thick. In the intra-atrial septum, immediately above the insertion of the atrioventricular valves, a round aperture, nearly 40 mm. in diameter, was found. The foramen ovale was open.

The lowest lobe of the right lung was divided into numerous accessory lobes. There was a fairly extensive paravertebral pneumonia with spots of atelectasis and subpleural hemorrhages. The left lung was divided into three lobes. Of these, both the lower and the middle lobe showed an indication of subdivision. There was an extensive pneumonia of the lower and middle lobes, and on both sides a mucopurulent bronchitis.

In the left pleural cavity, near the vertebral column, a tumor about the size of half an egg was palpable and protruded above the normal level of the diaphragm. This tumor proved to be the left kidney and the suprarenal gland and reached as far as the ninth rib.

In order to obtain adequate insight into the topographic relations in this region, microscopic sections were made of the kidney, suprarenal gland and diaphragm. In spite of the distention, the diaphragm proved to be unimpaired. There was thus no diaphragmatic hernia but only a dystopia of the kidney with the suprarenal gland into the thoracic cavity.

The microscopic sections of the skin were embedded in paraffin; hematoxylin-eosin and van Gieson stains were used. As expected, muscular tissue was found, in some places typically forming bigger and smaller bundles. Muscular tissue was thus found in the skin of the neck, where normally it does not occur. This is of great importance as support of the hypothesis that an abnormal direction of the platysma is the cause of pterygium colli, particularly as roentgenologic and clinical examination as well as necropsy all proved conclusively that only an abnormal condition of the skin could be the underlying cause, all the other muscles of the neck being normal.

The possibility that the muscular tissue belonged to the musculus occipitalis or musculus auricularis posterior may be excluded, since one of the two pieces was cut from the middle of the fold, and the utmost care was taken to use only the movable folds of skin for these examinations.

In some of the cases of pterygium colli reported in the literature, folds of skin at the shoulders and elbows also existed. It is most probable that here, too, the presence of muscular tissue in the skin is the cause of this deformity.

CONCLUSION

Pterygium colli congenitum must be considered a rare congenital deformity *sui generis*. In the case described, it could be ascertained that this malformation of the neck is not due to an anomalous condition of the long muscles of the neck, but is caused only by the skin, subcutaneous and fatty tissue, and the fascia colli superficialis. In the microscopic sections of the fold of skin, muscular tissue was found; probably a variation of the normal direction of the platysma is at the root of this deformity.

ACRODYNIA (SO-CALLED)

A STUDY OF THE PATHOLOGY *

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The clinical entity with which this report deals was first described about ten years ago. Since then it has been reported by observers in Australia, Europe and North America. There has been a difference of opinion as to a proper name for the disease. Although the literature on the subject is not particularly voluminous, a review of it will demonstrate clearly the causes for this lack of unanimity. The names most commonly employed at present are erythredema-polyneuritis, erythredema, pink disease, Swift's disease, acrodynia and Feer's disease. This multiplicity of names has grown chiefly out of insufficient information concerning the etiology, pathology, pathogenesis and even the clinical characteristics of the disease to classify it or to name it properly.

Weston,[1] who is responsible for the term acrodynia, which is probably the most widely used at present, applied it to a group of cases reviewed by Bilderbach.[2] In a superficial way, these exhibited some of the characteristics of a disease described by French authors in the early part of the nineteenth century. Swift,[3] in Australia, who had actually observed a large number of children with this disease, suggested the name erythredema, since this seemed to describe best the chief clinical features of the disease. One of his collaborators had already applied to it the name "pink disease." Feer,[4] apparently the first to describe the condition in Germany, decided from the clinical aspects that it was essentially neurosis of the vegetative nervous system; since his first report appeared, other German authors have added reports of cases which they termed Feer's disease. The term, dermatopolyneuritis, suggested by Thursfield and Paterson,[5] was later discarded by Paterson and Green-

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* Read before the Northwest Pediatric Society, Rochester, Minn., July 16, 1927.
* From the sections on Pathologic Anatomy and Pediatrics of the Mayo Clinic.

1. Weston, William: Acrodynia, Arch. Pediat. **37**:513, 1920.

2. Bilderbach, J. B.: A Group of Cases of Unknown Etiology and Diagnosis, Northwest Med. **19**:263, 1920.

3. Swift, H.: Erythroedema, Lancet **1**:611, 1918.

4. Feer, E.: Eine eigenartige Neurose des vegetativen System beim Kleinkinde. (Acrodynie, Erythrödem, Pink disease), Jahrb. f. Kinderh. **108**:267, 1925.

5. Thursfield, Hugh; and Paterson, D. H.: Case of Dermato-Polyneuritis, Proc. Roy. Soc. Med., Sec. Dis. Child. **15**:53, 1922.

field [6] (1923) in favor of the term erythredema-polyneuritis. This term and the erythredema of Swift have been agreed on by most of the later writers as the least confusing and the most descriptive.

Although reports of the disease have emanated from distant and widespread points, they have stated, with one exception, that it occurs in children from a few months to 7 years of age. The exception, a report by White,[7] dealt with two cases the identity of which certainly requires more evidence than was presented. Perhaps most cases have occurred in patients between a few months and 4 years of age so that, as the result of inability to describe the subjective manifestations, interpretation of them depends largely on the behavior exhibited by the children.

The symptoms, however, are extremely clearcut, although every patient may not display all the features that the disease is capable of manifesting. Indeed, the picture is so striking that the expression, "once seen, never forgotten," is frequently used in referring to it. As symptoms have been fully described by others and since the accompanying case report is typical, a discussion of the symptoms will not be included. Rodda [8] analyzed and grouped the symptoms conveniently under: (1) those general in nature, as anorexia, loss of weight and weakness; (2) those referable to the nervous system, as hyperirritability, sleeplessness, paresthesia, anesthesia, loss of reflexes, paresis, and photophobia, and (3) dermatologic symptoms, as hyperhidrosis, miliaria, desquamation, erythema, swelling, cyanosis, coldness, alopecia and ulceration of the gums with loss of teeth.

The etiology of the disease is not known. Infections, food deficiency, arsenical intoxication and neurosis of the vegetative nervous system have been suggested as etiologic factors. Lack of evidence in favor of arsenical poisoning and neurosis of the vegative nervous system has practically disproved these theories. There is abundant evidence against the theory of food deficiency. The preponderance of opinion regarding etiology at present favors infection, although it must be admitted that the evidence which has been brought forward in substantiation is in no way conclusive.

The prognosis is usually good. Recovery may not be complete before several weeks or months, but the little patients seldom succumb. If death does occur, evidence of intercurrent infection, chiefly bronchopneumonia, is usually found. In the ninety-one case reports reviewed

6. Paterson, Donald; and Greenfield, J. G.: Erythroedema Polyneuritis (the So-Called "Pink Disease"), Quart. J. Med. **17**:6, 1923.

7. White, C. J.: Acrodynia in Adults, J. A. M. A. **87**:1092 (Oct. 2) 1926.

8. Rodda, F. C.: Acrodynia: A Clinical Study of Seventeen Cases, Am. J. Dis. Child. **30**:224, 1925.

by Wood and Cole,[9] whose series is the largest reported, there were five deaths, four from bronchopneumonia and one sudden death ascribed to cardiac failure. The mortality rate, therefore, was about 6 per cent. The actual causes of death in the limited number of fatal cases reported by other authors is as follows: Byfield, (1920), four deaths, one from a deep phlegmon, one from advanced tuberculosis, and two from bronchopneumonia; Paterson and Greenfield, one from miliary tuberculosis; Brown,[10] two from bronchopneumonia; Zahorsky,[11] one from septicemia originating in a severe ulcer of the tongue; Thursfield and Paterson,[12] one from acute intussusception; Warthin,[13] two from bronchopneumonia, and one death in a case of Swift's mentioned by Wood as being due to sudden cardiac failure similar to that in one of his own. To this list we can add three deaths; the pathologic examination in one of these cases furnishes the material for this report.

NECROPSY DATA IN CASES REPORTED IN THE LITERATURE

In the series of five cases reported by Wood and Cole little except bronchopneumonia was found, and nothing characteristic of the disease was described in their report. Thursfield and Paterson's case, outside of acute intussusception "failed to reveal any gross abnormality." A limited examination in Davis'[14] case showed some fatty degeneration of the liver. From an examination in his two cases, Warthin reported:

> The essential pathologic changes in these two cases would appear to be extreme edema and slight meningeal irritation of the central nervous system, chronic erythema of the skin with hyperkeratosis, hypertrophy of the epidermis and sweat glands, with slight pigmentation of the rete, occurring in children of the hypoplastic lymphatic constitution, with associated or terminal respiratory infections and gastro-intestinal catarrh and inanition.
>
> These two cases, therefore, do not support the theory of a polyneuritis as the essential feature of the disease; neither do they justify the use of the term erythredema as a fitting designation, as they showed no edema of the corium They do not present any evidence as to a specific infectious etiology; they likewise show no relationship between tonsillar disease and the syndrome. The changes in the skin and nervous system suggested to me at once the pathology of the

9. Wood, A. J.: Erythroedema, M. J. Australia **1**:145, 1921.

10. Brown, Alan; Courtney, A. M., and MacLachlan, I. F.: A Clinical and Metabolic Study of Acrodynia, Arch. Pediat. **38**:609, 1921.

11. Zahorsky, John: Three Cases of Erythredema (Acrodynia) in Infants, M. Clin. N. Amer. **6**:97, 1922.

12. Thursfield, Hugh; and Paterson, D. H.: Dermato-Polyneuritis (Acrodynia: Erythroedema), Brit. J. Child. Dis. **19**:27, 1922.

13. Warthin, A. S.: So-Called Acrodynia Erythroedema (Swift's Disease): Pathologic Study of Two Necropsy Cases, Arch. Path. **1**:64 (Jan.) 1926.

14. Davis, C. M.: Acrodynia: Report of a Fatal Case, Arch. Pediat. **39**:611, 1922.

early erythema stage of pellagra. The changes in the skin are also identical with those seen in certain forms of light sensitization, xeroderma and fagopyrism. They are also identical with certain stages of roentgen-ray and ultraviolet erythemas. The entire anatomic picture in these two cases suggests either food deficiency or a toxic state acting on persons of the hypoplastic constitution, affecting the reticulo-endothelial system of the meninges and skin, the vegetative nervous system and possibly leading to a light sensitization. May it not be, as was early suggested by Byfield, a condition closely related to pellagra or, perhaps an infantile variety of that affection? Other necropsy cases must be collected and studied before this question can be settled. In the meantime, it would be better to call the condition Swift's disease than to designate it by terms that apply so little as do acrodynia or erythredema.

Byfield, in commenting on the necropsy data in his cases, stated:

In one case complicated by tuberculosis there was involvement of an occasional anterior horn cell of the spinal cord, gliosis about the central canal and edema of the sensory roots.

On the basis of a study of seventeen cases, he stated:

From these findings it seems probable that we are dealing with a primary disease of the nervous system. The falling out of the teeth (in three cases) without a distinct involvement of the gums, the falling out of the hair and a double neurokeratitis (first case) point quite clearly to an involvement of the fifth nerve. The paresthesia of the extremities and of the trunk also suggests a sensory nerve involvement, while the coldness and blueness of the finger-tips and toe-tips points to a vasomotor disturbance. The muscular weakness and atrophy, the diminution of the reflexes and, at times, their complete absence suggests involvement of the lower motor neurones, even though a complete palsy was not commonly encountered. In other words, there seems to have been a preponderance of sensory manifestations with a mild affection of motor nerves.

Paterson and Greenfield maintained that the microscopic appearance of the tissues of the nervous system in one of two patients examined proved conclusively that the disease is polyneuritis affecting particularly the peripheral parts of the nerve trunks. They found considerable myelin destruction in some fibers of the peripheral nerves, increasingly marked toward the periphery. The gray matter of the central nervous system showed a diffuse increase of small cells. There was also some cellular increase in the nerve roots. Some of the motor nerve cells of the ventral horns showed moderate perinuclear chromatolysis, eccentricity of the nucleus and large vacuoles in the cytoplasm. These authors had difficulty in deciding the nature of the cells which gave the appearance of cellular infiltration of the nerve roots and of the gray matter of the cord. Those in the nerve roots, it was felt, appeared to be derived from the nucleated sheath of Schwann; those in the cord suggested glial origin. Although these authors did not find evidence of bacterial invasion of either the central or the peripheral nervous system, they stated that the disease is polyneuritis similar to, but to be dis-

tinguished from, the "acute infective polyneuritis" of Bashford,[15] and probably due to the toxins of some micro-organism.

REPORT OF A CASE

A boy, aged 23 months, was admitted to the Mayo Clinic, March 8, 1927, because of fever, sore mouth and a rash, all of which had been present for three weeks. The family history was not significant. The child had had pertussis and bronchopneumonia six months previously; convalescence had proceeded uneventfully. Five weeks before admission the local physician had diagnosed acute tonsillitis, recovery from which had seemed protracted. It had been noted that the child was biting the fingers, but particular attention had not been paid to this behavior. Two weeks later a punctate rash had appeared on the wrists, dorsum of the feet and abdomen, and had gradually become generalized. One week before admission the lips had become swollen. Three days before admission stomatitis, gingivitis and loosening of the teeth had been noted. The day before admission the right eye had become red. The child had become fretful and irritable, scratching the hands and feet almost continuously and occasionally pulling the hair. There had been slight fever.

The child was fairly well developed and well nourished; he assumed a knee-chest position with the face buried in the bedclothes because of photophobia. He was fretful and irritable and appeared to be in great discomfort. There was a generalized papular and papulopustular eruption, more marked on the hands and feet which were swollen and erythematous. Marked gingivitis and stomatitis were present. The teeth were loose and lying in a mass of necrotic tissue. The throat and tonsils were slightly reddened. The general restlessness and tremor were suggestive of mild encephalitis. Lack of reaction to a pin prick demonstrated decreased acuity of sensation. The gait was wobbly or ataxic. The laboratory tests were negative except that the leukocytes numbered 17,000, with a normal differential count.

The course in the hospital was uneventful until the eleventh day, when there was a sudden rise of temperature to 103 F. A few râles were present in both lungs. Dyspnea and cyanosis with sudden death occurred within a few hours.

SUMMARY OF DATA OBTAINED AT NECROPSY

Necropsy was performed two hours and fifteen minutes after death. Slight generalized scaling of the skin, most marked on the hands and feet, especially on the palmar and plantar surfaces was found. A few small ulcerated areas were present on the third finger and back of the right hand. Hemorrhagic, ulcerated areas were present on the lips, and there was stomatitis and gingivitis, the gums being necrotic and the teeth either loose or absent. Edema, ascites, hydrothorax and hydropericardium were not noted. A gross lesion was not present in the heart. There was bilateral bronchopneumonia of slight extent. The liver showed fatty change and a small hemangioma. In spite of the short period between death and the necropsy, there was an area of postmortem digestion at the cardia of the stomach, and about 30 cc. of gastric contents was present in the left upper quadrant of the peritoneal cavity. The remainder of the gastro-intestinal tract was normal except for slight prominence of Peyer's patches of the ileum and of the solitary lymph follicles of the colon. The other organs did not show any gross

15. Bashford, E. F.; Bradford, J. R., and Wilson, J. A.: Acute Infective Polyneuritis, Quart. J. Med. **12**:88, 1918-1919.

lesion. The brain and spinal cord were entirely normal on gross examination, as were the various peripheral nerves examined.

Results of microscopic studies of the organs of the chest, abdomen and pelvis were negative except that it was found that the lungs showed evidence of bronchopneumonia and the liver showed vacuolization of some cells containing fat. There was also a small hemangioma in process of formation. Hematoxylin and eosin, Weigert's myelin-sheath stain, Orlandi's modification of Bielschowsky's stain, scarlet red, Marchi, Nissl and various modifications and combinations of these stains were used in studying the tissues of the nervous system.

Peripheral nerves from the extremities showed varying degrees of fragmentation of the myelin sheaths in different places, especially in the sciatic and femoral nerves, but little in the nerves originating in the brachial plexus of either side. These changes were best seen in the right femoral nerve in which the Weigert stain showed slight evidence of demyelinization; scarlet red, and Marchi stains

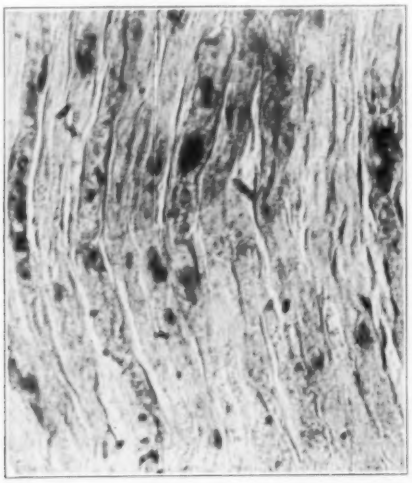

Fig. 1.—Right femoral nerve showing early degeneration of the myelin sheaths. The degenerating sheaths stain as black droplets or granules. Marchi stain; × 300.

revealed this as an extensive process (fig. 1), whereas the Orlandi stain showed the axis cylinders to be irregularly swollen. In a section stained by a combination of scarlet red and Orlandi, the greatest amount of free fat was present in those areas in which the axis cylinders were swollen, nodular and apparently broken. In the dorsal root ganglions of the lumbar regions, some of the ganglion cells showed evidence of chromatolysis (fig. 2); the Nissl granules had either disintegrated and disappeared or were absent from the center of the cell and collected at the periphery. In these cells the nuclei were eccentric and oval, and were flattened against the periphery of the cells or were even protruding through the cell membrane. In some, the nucleus was missing, and the Nissl granules completely disintegrated, only the swollen cell outline remaining; sometimes even this was indistinct. In the dorsal root ganglions of the thoracic region these changes were not so pronounced, while the dorsal root ganglions of the cervical region were not obtained. In the sacral region of the spinal cord, there were degenerative changes in some anterior horn cells, especially in the ventrolateral group (fig. 3),

Fig. 2.—Dorsal root ganglion from the lumbar region. Chromatolysis in two cells with eccentricity of the nuclei of which one is bulging through the cell membrane; the cells are obviously swollen. Thionin stain; × 300.

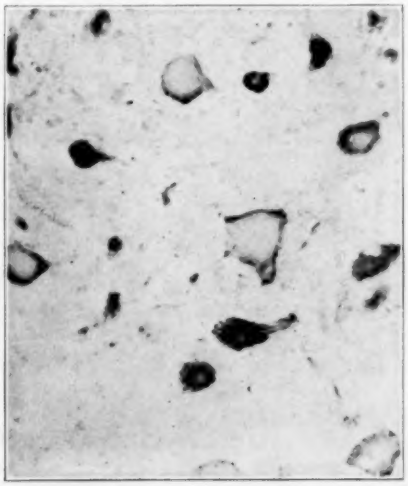

Fig. 3.—Anterior horn ganglion cells of the ventrolateral cell group of the spinal cord (sacral); large, swollen, degenerating and degenerated cells showing chromatolysis with eccentricity or extrusion of the nucleus. Normal cells can also be seen. Thionin stain; × 100.

which showed chromatolysis, swelling of the cells and eccentricity of the nucleus even to the point of extrusion or disappearance. Most of the other cell groups seemed to have escaped. In the upper lumbar region chromatolysis of the ventrolateral cell column involved only one side and was not so extensive as in the sacral region, but the cells affected were severely damaged. In the thoracic region, the anterior horn cells did not show any change, but the lateral horn cells on both sides were chromatolytic, and the cells of Clarke's column were involved to a lesser degree.

It was interesting to note that the fiber tracts of the spinal cord did not reveal any apparent change in the myelin sheaths or axis cylinders, but there was an apparent increase in the number of glial cells in the areas of the spinal cord in which the ganglion cells showed chromatolysis; however, in no level of the spinal cord, or in the dorsal root ganglion cells, or peripheral nerves was there evidence of acute or chronic inflammation. The changes seemed to be due to

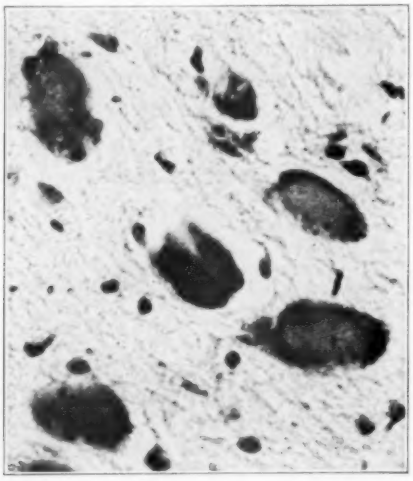

Fig. 4.—Cells of the locus caeruleus showing degenerative changes with neurophages and satellitosis. Chromatolysis and eccentric nuclei are shown. Thionin stain; × 300.

axonal degeneration rather than to primary chromatolysis, as the cells involved were scattered, no single cell group being completely involved. Some nerve cells were involved but the larger number were normal; infection was not present anywhere in the central nervous system, and the spinal cord showed chromatolysis of those cells with the long axons to the limbs. The change in the cells was similar (for the most part) to that accredited to the axon reaction, although some cells showed more profound chromatolysis and extrusion of the nucleus.

Examination of the medulla oblongata, midbrain and basal nuclei gave more or less support to this theory. In the floor of the fourth ventricle chromatolysis of the cells was more general in the eminentia teres, in the mesencephalic root of the fifth nerve and particularly in the locus caeruleus. Extensive advanced chromatolysis was found in these nuclei; scarcely a single cell escaped and some were almost completely disintegrated, with vacuolization and satellitosis (fig. 4).

Similar changes were found in some of the cells of the lenticular nucleus and in the anterior nucleus of the thalamus.

The gasserian ganglion on both sides, but especially the right, showed more extensive chromatolysis of many nerve cells (fig. 5) than in the dorsal root ganglion of the spinal cord. In some of these cells, the degeneration was extreme; the Nissl bodies and the nucleus had disappeared, leaving only a faint cell out-

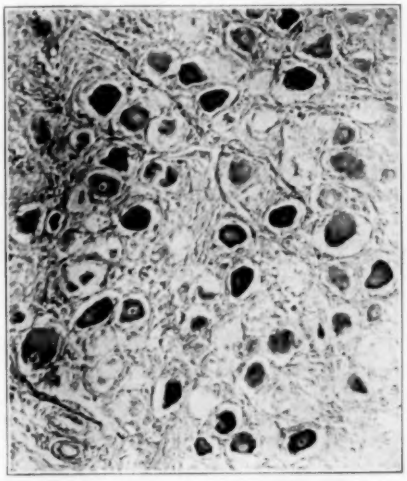

Fig. 5.—Nerve cells of the right gasserian ganglion. Many cells in various stages of degeneration can be seen. Thionin stain; × 100.

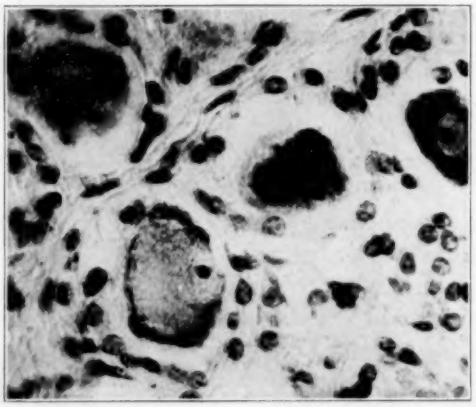

Fig. 6.—Left gasserian ganglion. Two cells show chromatolysis with collections of the chromatin substance at the periphery of the cells, which are swollen, and eccentricity of the nucleus, which is oval in shape. Thionin stain; × 300.

line (fig. 6). Other cells retained the nucleus at their periphery, and the chromaffin substance was collected in masses underneath the cell membrane with a clear area at the center; other cells showed vacuolization. In spite of these changes, many normal cells remained.

The cells of the cortex of the brain seemed to have escaped the degenerative process which was limited to the basal nuclei, the midbrain, medulla oblongata, gasserian ganglions, and some cells of the spinal cord, dorsal root ganglions and peripheral nerves.

As would be expected from the clinical examination, not any group of cells was entirely destroyed, but the chromatolysis involved some cells in many groups. There was little evidence to be gathered from this case as to the ultimate fate of the nerve cells showing advanced chromatolysis, although some would never have regenerated on account of the extrusion of the nucleus and the severe injury inflicted. It was unfortunate that this study was not so complete as to include an examination of the vasomotor and sympathetic nervous systems, especially the nerves supplying the abdominal and thoracic viscera.

COMMENT

These changes in the nervous system are of interest in view of the observations of other investigators. Not many have thoroughly examined the nervous system, but Byfield and Paterson and Greenfield found similar changes in some of the anterior horn cells of the spinal cord, while the latter found degenerative changes in the peripheral nerves, more accentuated toward the distal portions.

In our case it was not possible to examine the more distal parts of the nerves, but the proximal portions showed changes similar to those of Paterson and Greenfield. Warthin did not find any changes in the nervous system except edema of the meninges. Mention is not made by any observers of changes in the dorsal root ganglions such as we saw, nor of changes in the gasserian ganglions. Paterson and Greenfield did not find changes in the central nervous system above the level of the cervical cord. Hence, there is agreement in the three reports that: (1) There is a degenerative process affecting the central and peripheral nervous systems. (2) This is evident in the spinal cord as chromatolysis of some of the anterior horn cells. (3) The cerebral cortex and cerebellum do not participate in these changes. Our case differs in that there were changes in the basal nuclei and in some of the nuclei of the medulla oblongata. Other points of difference are that the gliosis around the central canal of the spinal cord in our case was no more pronounced than normal, nor was the number of glial cells throughout the spinal cord increased above normal, which is greater in children than in adults. In our case there was no increase, other than an apparent one, in the number of nuclei of the sheath of Schwann.

CONCLUSION

It is impossible to draw many definite conclusions from the appearance of the tissues in this case. However, in the light of these data and the reports by Byfield and by Paterson and Greenfield, it would

appear that the central nervous system is affected to a large extent, and probably to a greater extent than other parts of the body, in the essential process. Note must be made of the fact that in one or two instances in which the central nervous system has been examined nothing of importance has been found except a slight meningeal change by Warthin. There is a difference of opinion in regard to the exact nature of the changes in the skin, and nothing of significance has as yet been brought to light by examination of the skin. That profound changes occur in the central nervous system of some, if not all, patients seems to be true. These may be missed by insufficient examination, especially if microscopic studies are not made.

The cause of the changes recorded in this case and in those of Byfield and of Paterson and Greenfield cannot be stated. If one studies the writings of Bradford, Bashford and Wilson, on the basis of which Paterson and Greenfield compare their data with those of acute infectious polyneuritis, it will be evident that there are many points on which the clinical manifestations and pathologic changes differ. The frequent association of this disease with infection of the upper respiratory tract and the degenerative character of the changes in the nervous system favor the view that the disease is an infection, the toxic products of which secondarily affect other parts of the body.

VINCENT'S INFECTION OF THE NOSE

REPORT OF A CASE *

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Bloody nasal discharge, particularly when it has been persistent, is so often associated with diphtheritic inflammation and foreign body that little attention is usually paid to other possibilities. The importance of ruling out diphtheria is obviously of prime concern. A foreign body, though requiring removal, is fraught with less immediate serious consequences. The possibility of rarer conditions, such as the granulomatous infections—syphilis and tuberculosis—must always be considered.

The following case is of more than usual interest; first, because of the rarity of occurrence of this condition (only one previous case having been mentioned,[1] to my knowledge) and second, because of the ease with which the diagnosis can be made and confirmed, if only the condition is kept in mind.

CASE REPORT

History.—D. M., a boy, aged 3 years, of Italian parentage, was admitted to the children's medical division of Bellevue Hospital, on the night of Oct. 27, 1927. The family history was unimportant. The developmental history was normal.

He had measles when he was 2 years old, and pneumonia complicated by empyema eight months before admission; thoracotomy was performed, after which he was confined to bed for three months.

He was well until six days before admission, when he began to have persistent bloody discharge from the left nostril as the outstanding complaint. The discharge was not only bloody but was mixed with a mucopurulent material and had a fetid odor. The amount of blood in the discharge would vary, but was most always present. The skin about the nostril became excoriated, and two days later there was a noticeable swelling of the cervical nodes on the left side of the neck. The following day, three days after the onset, the left half of the upper lip became swollen, and bleeding from the gums occurred. By this time there was considerable excoriation of the skin of the upper lip. Restlessness, disinclination for food, and foul odor of the breath were constantly present. Previous injury, exposure to any infectious or contagious diseases or bleeding on any previous occasion had not occurred.

Physical Examination.—On admission, the child was fairly well developed and nourished, of pasty complexion, prostrated, irritable and apparently somewhat toxic. There was a definite swelling of the lymph nodes of the left side of the neck, marked swelling of the upper lip and alar region of the nose and a profuse

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* Received for publication, March 8, 1928.

* From the Department of Diseases of Children, College of Physicians and Surgeons, Columbia University, and the Children's Medical Division of Bellevue Hospital, New York City.

1. Place, E. H.: Vincent's Angina, Boston M. & S. J. **164**:720, 1911.

left nasal sanguinopurulent discharge. The child was acutely ill and it looked like he had nasal diphtheria.

The head, eyes and ears were normal.

Nose: The discharge from the left nostril was a mixture of blood and mucopurulent material and contained some greenish sloughlike shreds and had a fetid odor. The skin around the nose was excoriated, and there was a fissure at the outer angle of the left nostril.

Lips: The left half of the upper lip was markedly swollen, the swelling extending well onto the cheek of the same side. A greenish-yellow membrane almost completely covered the mucous surface of the upper lip, particularly at the left side. Bleeding was easily induced by examination. The lower lip was not swollen, and aside from a slight redness was normal.

Mouth: The gums were congested and bled when touched. A few small irregular whitish areas were seen on the margin of the upper gums between the teeth. These areas were mostly limited to the left side. The membrane described on the mucous surface of the upper lip seemed to be almost continuous in places, with a sloughing membrane of the upper gums. The condition of the teeth appeared to be good.

Tonsils: The tonsils were small and were not diseased and did not give evidence of involvement. The pharynx and palate seemed clear.

Neck: The left submaxillary and submental glands were much enlarged and tender. The left anterior cervical glands were also enlarged but apparently not tender.

Chest: Nothing unusual except the scar of the recent thoracotomy was found. The lungs were normal.

Heart: The rate was rapid but regular; the sounds were of poor quality and there was no murmur.

Abdomen and Extremities: The abdomen and extremities were normal.

Swelling of any of the other peripheral lymph nodes of the body was not found.

On admission, the temperature was 101.3 F., the pulse rate 136, and respirations, 32. The weight was 25 pounds (11.3 Kg.). Cultures and smears from the nose, lips and gums were taken, and 20,000 units of diphtheria antitoxin were given in the gluteal muscles. Direct smears from the nose, lip and gum showed an enormous number of fusiform bacilli and spirilla. The methylene-blue stain was used. To check the symptoms, other smears from the nose were again immediately taken, and each showed the Vincent's organisms in abundance.

Treatment was begun at once. The nose was swabbed with half strength hydrogen peroxide, then dry swabbed and followed by the application of 5 per cent chromic acid which was kept in the nostril for a full minute. This was done subsequently twice a day. The lips and gums were treated in like manner. The excoriated skin was well annointed with 5 per cent ammoniated mercury.

Bromides were given for restlessness.

The diet consisted chiefly of forced fluids, and later soft solids were added as the condition improved. It is important for the comfort of the patient that all foods be given cold.

Course of the Disease.—On Oct. 28, 1927, cultures from the nose and throat were reported negative for diphtheria. The general condition of the child was about the same; the temperature was still 101 F., and the pulse rate, 120. He did not show evidence of dysphagia. The nasal discharge was still profuse but the parts, as a whole, looked a trifle cleaner. The profuseness of the discharge inter-

fered with an accurate examination of the nasal cavity by the rhinologist. The child was still restless during the night but slept more than on the previous night.

On October 29, the temperature was 100 F.; the pulse was still rapid, the rate being 120. Clinically, the child showed improvement. He now sat up, became interested in things and continued not to show any difficulty in taking food. The nasal discharge was still blood streaked but was not as profuse, and the swelling of the upper lip seemed to have subsided somewhat.

The child was seen by the dentist, who said that the teeth were in good condition and apparently unrelated to the oral infection.

During the day, the nurse reported a stool with some blood and mucus, which, unfortunately, was not saved. Subsequent stools, however, were normal. Smears from the nose and gums showed organisms in decreasing numbers and poorly stained. A second culture from the nose and throat was negative for diphtheria. That night the patient slept fairly well, though he was still restless.

On November 1, the temperature was down to 99 F., the pulse rate was 90, and respirations, 22. The general condition was good. The nasal discharge was slight and was no longer blood streaked. The gums and lips were much cleaner looking, and the swelling of the lip and cheek was almost entirely gone. The glands were still large but no longer tender.

Nasal irrigations of sodium perborate were now substituted for the chromic acid treatment. This was done four times a day with a solution made up of 1 drachm (3.9 Gm.) of sodium perborate to 8 ounces (236 cc.) of water. Treatment of the mouth was not changed and potassium permanganate, 1:5,000, was introduced as a mouth wash every hour.

For the first time smears of the nose were negative for Vincent's organisms. Smears of the gums showed only a few fusiform bacilli and some poorly staining spirilla.

On November 7, the nasal discharge had entirely subsided, and smears of the gums were now negative for Vincent's organisms.

The general condition of the patient remained good. The swollen appearance of the left side of the face had entirely disappeared, and the cervical glands were much decreased in size.

Laboratory Examination.—On October 27, the systolic blood pressure was 60; diastolic, 35 mm. of mercury, apparently an index of the prostration that accompanied the infection.

Examination of the blood showed: White blood cells, 16,000, with 75 per cent polymorphonuclears. The Wassermann reaction was negative.

The urine was normal on repeated examination.

The Schick and tuberculin ($\frac{1}{20}$ and $\frac{1}{10}$ mg. intradermally) tests were negative.

Roentgen-ray examination of the teeth gave negative results. Roentgen-ray examination of the sinuses showed a diminution of illumination of both maxillaries.

The patient was discharged as cured on Nov. 15, 1927, weighing 27 pounds and 12 ounces (12.5 Kg.), a gain over his weight at admission of 2 pounds and 12 ounces (1.2 Kg.) in nineteen days.

COMMENT

That this condition should be so rare is unusual when one considers the ease with which mucous membranes in other localities are affected

by these organisms. Vincent's infection of the gums, lips, tonsils, uvula, tongue, pharynx, soft palate and buccal mucosa is well known.

Place,[1] in a study of Vincent's angina in which he includes eighty cases in children, mentioned only one patient with Vincent's infection of the nose who showed marked caries, sanguineous discharge and foul odor of the breath. This patient had an associated infection of the gums also.

A careful review of the literature to date does not reveal a subsequent or previous report of a similar case or cases. Textbooks do not mention the nose being susceptible to Vincent's infection, nor is the condition included as a possibility in a differential diagnosis dealing with sanguineous nasal discharge.

That Vincent's organisms are rare in adenoid tissue was shown by Davis and Pilot.[2] This observation, coupled with the fact that the nasal passages are most always filled with oxygen, which is detrimental to the existence of these anaerobic organisms, may have some bearing on the rarity of the condition. It may well be asked why, then, these organisms are so prevalent in the mouth in which aerobic conditions exist. The probable explanation is that Vincent's organisms, as was shown by Davis and Pilot, inhabit the tonsillar crypts, which may be covered over by exudate or a thin film, the dental cavities and the crevices of the teeth just under the free margin of the gums in which anaerobic conditions exist.

In view of this case, it appears possible that in other patients with Vincent's infection of the nose the condition has gone unrecognized because it is not suspected. This case emphasizes the importance of taking nasal smears as a routine measure in patients with sanguineous nasal discharge. These organisms are anaerobic and will not grow on the ordinary culture mediums.

That a positive nasal culture for diphtheria does not exclude the possibility of a concomitant Vincent's infection is evidenced by Spray's[3] report of a case in which a direct smear of the throat showed fusiform bacilli and spirilla in abundance, and in which on the next day, culture was positive for diphtheria bacillus.

SYMPTOMS

It appears that the symptoms of a Vincent's infection of the nose are characterized by a persistent sanguineous mucopurulent discharge with a greenish membranous slough. The discharge has a fetid odor

2. Davis, D. J., and Pilot, Q.: Studies in Fusiform Bacillus and Vincent's Spirochete, J.A.M.A. **79**:944 (Sept. 16) 1922.

3. Spray, R. S.: Coincident Diphtheria and Vincent's Angina, J.A.M.A. **88**: 1234 (April 16) 1927.

and tends to excoriate the skin. The nose is tender to touch, rendering examination difficult. The condition may be associated with Vincent's infection of the gums. There is an accompanying cervical adenitis.

Slight elevation in temperature, rapid pulse, irritability and restlessness occur.

CONCLUSIONS

1. A case of Vincent's infection of the nose in a child, aged 3 years, is reported.

2. Its close resemblance to nasal diphtheria is emphasized.

3. In any persistent sanguineous nasal discharge, Vincent's infection of the nose is to be considered. The ease with which a diagnosis can be established makes a routine smear valuable in these cases.

Progress in Pediatrics

CONDITIONS LEADING TO PRESCOLIOSIS

A PROBLEM IN PROPHYLAXIS *

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The realization that an established curvature of the spine in its full clinical form is, in the anatomic sense, an incurable condition has prompted intensive search for remote and early causes of the deformity in the hope that early diagnosis would open the way for prevention. The practical result of this movement was the establishment of medical supervision of school children which was inaugurated because the impression existed that a large portion of the deformities of the spine developed during school years. It was expected to strike at the very root of the pathogenesis of this condition. Undoubtedly, school inspection has done a great deal of good in cases of curvature of the spine in that early cases of deformity are discovered and early and more efficient treatment is therefore possible. From this point of view, such inspection must be encouraged.

So far as real prevention of the deformity is concerned, however, there is no question that the results of school inspection have fallen short of expectations. This is due, in my opinion, to the fact that inspection is not practiced at the clinical age at which the beginnings of the deformity occur.

The deeper one goes into the study of the factors leading to the deformity, the more one becomes convinced that the ultimate causes appear submerged in general systemic conditions of the organism. Because these so intimately involve the body as a whole, the problem of prophylaxis and prevention of deformities of the spine becomes of even greater interest to the general practitioner than to the orthopedist. It becomes necessary to give due cognizance to alterations in the general health which precede the appearance of definite symptoms. In the majority of cases of scoliosis, even in a great majority of the cases of anteroposterior curves of the spine, there is a time in life when apparently complete and stable symmetry of the body exists. The deformity develops insidiously from a state of complete physical balance, and insidiously grows greater and greater. It appears, then, that some children are unable to resist the ordinary strains and stresses to which the human body is subjected in the performance of its normal and physiologic tasks. In general terms this incongruity between the

* Received for publication, April 17, 1928.

demands of weight-bearing and dynamic stresses produced by the living and moving body and the natural resistance of this body against these stresses is designated as insufficiency or inadequacy of the spine.

Research leading to the recognition of a prescoliotic stage involves the formulation of a better definition of the causes which produce this inadequacy of resistance. How does scoliosis manifest itself in terms of general health, and when does it make its appearance?

For the great class of cases of lateral curvature of the spine, two exceptions must be made to the general premises under which a state of complete body balance was assumed to precede the development of the curvature: In the case of congenital curvature, there never is, in extrauterine life, a normal condition of the spine which would place it under the same conditions of resistance to weight-bearing forces as the normal spine. In the case of paralytic curvature of the spine, the normal physiologic resistance of the spine against external forces has become suddenly and rudely destroyed by the intercurrent disease which attacks the muscular apparatus of the trunk and other portions of the body. In these two conditions also one may speak, in a sense, of a prescoliotic stage, because a certain degree of balance and symmetry is maintained by the reserve muscular forces; in the first condition for a certain period after birth, and in the second, for a certain period after the onslaught of the disease, so that here also it may be said that the deformity develops after a period of latency. So far as the underlying pathologic causes are concerned, those which form the basis of the known types of scoliosis are easily discovered since in congenital, paralytic and the early rachitic types of scoliosis, the onset of the deformity coincides with the appearance of definite symptoms of the underlying systemic disease.

The prescoliotic stage, therefore, signifies a clinical period of latency during which the underlying pathologic conditions, such as congenital malformations, rickets, habitual posture, etc., are present, but no unmistakable signs of scoliosis have appeared. The recognition of this prescoliotic stage is of the greatest importance, because it is during this period, and not in the early stages of scoliosis itself, that the most effective prophylaxis against scoliosis can be accomplished.

In congenital scoliosis, no real prescoliotic stage exists as has already been pointed out; definite asymmetry of the spine, however, is a congenital factor which has existed since birth. Often there is a long period of latency, the spine remaining under muscular control in spite of its anatomic handicap. Clinically, the prescoliotic stage manifests itself in occasional abandonment of symmetry, the assumption of asymmetric posture for a short time. In acquired scoliosis, however, a definite prescoliotic stage exists, although it is difficult to determine its beginning. It is best to date it from the occasional and still controlled postural and attitudinal anomalies. The scoliosis itself begins with the assumption of habitual and not occasional asymmetric attitudes. A child who per-

sistently assumes such asymmetric positions from which it is becoming more and more difficult to arouse him is already in a state of scoliosis. It is the occasional anomalous attitude, sometimes not even of the scoliotic type, which must be regarded as the forerunner of scoliosis. It was observed that a child with poor erectors of the trunk inclines his body forward when sitting. This is a prescoliotic condition, because this attitude predisposes the patient toward the coming lateral deformity.

Fig. 1.—Congenital scoliosis; prescoliotic stage.

To these different anomalous attitudes belong the different positions of rest and relaxation manifested in standing, sitting, lying or walking. Until recent years it was believed that the habit of assuming such asymmetric postures, especially when sitting, was formed during school years. The condition was spoken of as a school scoliosis, which meant attitudinal anomalies which might lead to true scoliotic changes. Now it is known that these attitudinal anomalies really occur much earlier, during preschool years. The rapid growth during school years accentuates the tendency to faulty attitude; it increases the opportunity for fatigue and

muscle exhaustion. Faulty posture in writing, faulty attitude in standing, asymmetric carrying of books, etc., are contributary factors. They are, however, not true factors of the real prescoliotic stage, but are operative during the development of the deformity.

The gait is another predisposing element to which little attention has been paid until recently. The female pelvis, which during the phases of the gait makes a greater excursion than that of the male, is more affected by this dynamic element. The normal spine is able to compensate for the pelvic tilt if the body is held erect. Occasionally, however, a spine will lose its erect posture, and then one may consider that a prescoliotic stage exists. This asymmetry which becomes more and more

Fig. 2.—Rachitic scoliosis; prescoliotic stage. Note posture.

habitual, is increasingly less controlled by the muscles and is followed by a stage of scoliosis.

Of greatest clinical interest is the so-called rachitic prescoliotic stage which starts as an anteroposterior curve in the lower dorsal vertebra occurring at the time when the attitude is assumed, and which is one of the early signs of spinal rickets. The subsequently developing musculature straightens out many of these curves; others are compensated for by a converse curve which develops below the first curve. The round and hollow rachitic back is an example of the latter event. Occasionally, however, the musculature is too weak to effect compensatory adjustment. According to Farkas, in these cases the body automatically rotates around

to counteract and to check the tendency to forward flexion, so that the flexion deformity existing in the lower dorsal vertebra and lumbar spine by virtue of this twisting motion becomes the curve in the frontal plane which is called scoliosis. This explains the fact that many of the rachitic curvatures of the spine seen in young children are preceded by anteroposterior curves. In this conversion of the anteroposterior curve into a lateral curve by rotation of the body, one may see an illustrative example of a definite prescoliotic stage. The chain of events is as follows: At first there exists a total kyphotic deformity which is the normal attitude of the child as he learns to sit. Rickets supervenes, and the kyphotic curve becomes accentuated in the dorsolumbar region where the pressure is the greatest; thus the typical rachitic anteroposterior curve is formed. The dorsolumbar kyphosis persists after the child has begun to stand and walk. This kyphosis is the remainder of the total kyphosis which was natural in the child while sitting. When compensation of this kyphosis cannot be accomplished, the danger of forward flopping of the spine becomes increased. Then the child enforces its upright position only by the rotatory twist of the body. If, on the other hand, he succeeds in compensating for the anteroposterior curve by developing a round, hollow back, his spine is comparatively safe against lateral deviation. If the effort at compensation fails, the flat back results. This is unsafe, and a lateral curvature of the spine is prone to develop.

In paralytic scoliosis, it is difficult to determine the prescoliotic stage. A normal spine not inclined to lateral deviation from any of the causes mentioned, is suddenly afflicted by partial or complete loss of the use of its musculature. In its mode of development, this curvature simulates the physiologic scoliosis. Habitual weakness of the muscles now exists. Paralytic scoliosis is also of the so-called inclination type, that is, the deviation occurs first from segment to segment about a point of inflection. This form of scoliosis also develops so insidiously that it is difficult to distinguish between propensity and necessity. Often there is a long period of latency, sometimes extending over many years, during which the only sign of scoliosis observed is the occasional assumption of an asymmetric attitude. In all cases of extensive paralysis, the stability of the spine must be suspected, and the slightest defect of muscle control should be taken seriously, for when the scoliotic stage is entered in this type of curvature, the progress of deformity is rapid.

Little is known of the prescoliotic stage in empyematic scoliosis, that is, scoliosis following empyema. In type of development it is also inclinatory, that is, segment inclines against segment over a point of inflection, and the deformity develops from the effect of an unequal interthoracic pressure. In this condition, it is difficult to determine

just when active control of the spinal movement becomes embarrassed. In this form of scoliosis also it is best to date the prescoliotic stage back to the time of the original affliction of the lung.

PROPHYLAXIS

Recognition of the prescoliotic stage is essential for proper treatment, because if prophylaxis is to be timely, it must operate during the pre-scoliotic stage.

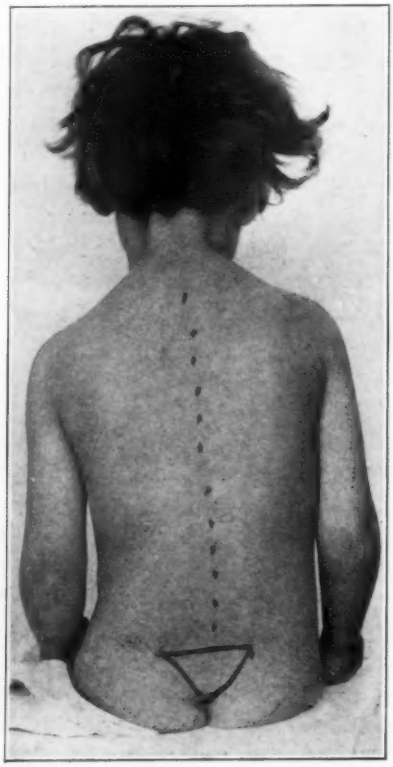


Fig. 3.—Paralytic scoliosis; prescoliotic stage. Slight asymmetric attitude.

It has been stated that the pre-scoliotic stage is characterized by anomalies in carriage and posture. If one seeks the causes of these early anomalies so far as they appear in general systemic conditions, they may be distinguished as follows: There is a general muscular weakness which dates back to the first month of extra-uterine life or which may even be a congenital condition. Feeding trouble and metabolic disturbances of all kinds have a decided influence on the development of the musculature and, indirectly, on the predisposition to static deformities of the spine.

Obstruction of the upper portion of the air passages and infection of the paranasal sinuses, tonsils and adenoids are also potential causes of weight-bearing anomalies of the spine. Aside from the fact that these conditions greatly influence the general tone of the muscles, together with the general health of the patient, they also have a direct deforming effect in inhibiting and impairing free respiration. The exercise of the normal respiratory function is an important factor for general health as well as for maintenance of normal carriage and posture even at the early age at which the period of prescoliosis occurs. Concern for the proper development of the respiratory function is as much a part of the physicians' duty as the establishment of normal metabolic function; this means proper feeding and elimination so far as the proper metabolic balance is concerned; proper hygienic measures, fresh air and suitable exercises so far as respiratory and muscle balance of the body is involved.

In the congenital type of scoliosis in which one cannot properly speak of a prescoliotic stage, a great deal of preventive work can, nevertheless, be accomplished, considering the long period of latency during which the spine is able to maintain its equilibrium against the odds of asymmetric weight-bearing. A great deal depends on the location of the congenital anomalies. Wedge formations or other anomalies in the lower part of the spine offer a less favorable outlook for maintenance of balance than those located at a higher level. It must be remembered, however, that the normal spine has enough reserve force to maintain its balance even against a certain degree of asymmetric construction.

The lack of symmetry acquired and leading to rachitic scoliosis is due to faulty attitudes and postures in positions of rest, such as forward flexion in sitting or lateral bending in children who are carried on one arm. The deformity becomes functional or attitudinal during a considerable length of time, and this period allows ample opportunity for the application of preventive measures. Prophylaxis involves not only a general antirachitic regime, but also local treatment of the musculature by massage and manipulation to secure the best degree of stability of the spine. Children with posterior deformities of the spine should not be encouraged to sit too soon and should be carried on a board or plaster bed rather than on the arm.

Of all types, habitual, idiopathic scoliosis has received the greatest attention, but the interest manifested in school children between the ages of 8 to 14 years who have this condition is decidedly belated. One must remember that a child who assumes an asymmetric attitude from which it is being aroused only with greater and greater difficulty is already a scoliotic child. The fight against scoliosis of the habitual type, therefore, should begin before school age as in the rachitic and other types. According to the most careful observations, the influence of the

school is that of an accentuating and aggravating element, but it is not in itself a causative factor. In examining a number of school children, Scholder found that from 20 to 30 per cent showed functional scoliosis as a result of faulty posture assumed by the child during or before school years. A critical period in the habitual type of scoliosis is that of rapid growth between the ages of 3 and 5 years, and it is at this time that prophylactic measures should be instituted. Postural exercises should be taught and other general measures taken to prevent the occa-

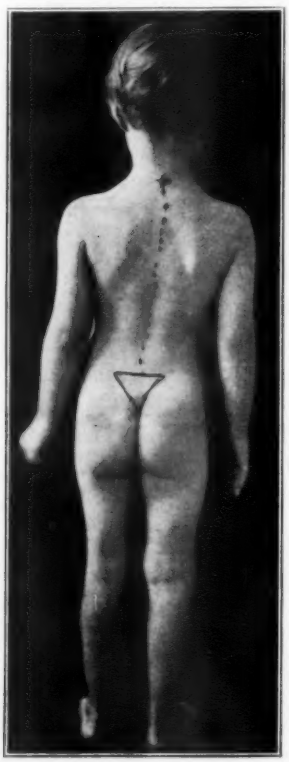


Fig. 4.—Habitual scoliosis; prescoliotic stage, beginning of asymmetric attitude.

sional faulty attitude which occurs at this age from becoming habitual. Between the ages of 8 to 14 years, there must be a proper supervision of posture during school hours; still more important, shortening of school periods, that is, the introduction of appropriate physical exercises of general character, should be given serious consideration.

In paralytic scoliosis it is difficult to speak of prophylaxis; yet in this condition also there is a long interval of complete latency between the onset of paralysis and the appearance of scoliosis. In cases of

extensive paralysis of the lower extremities, it is best to reckon with the possibility of subsequent scoliotic deformity, so that precautionary measures can be undertaken as a matter of routine. Unilateral weakness, paralysis or slight differences in the muscle strength of the two sides of the back or unilateral paresis of the muscles which lead to paralytic scoliosis are much harder to recognize than general weakness. Symmetrical paralysis of the muscles of the back or of the abdomen usually result in an anteroposterior curve. It is well known how irresistibly this type of deformity progresses, and therefore even the slightest suspicion of weakness or asymmetry of the back must indicate definite measures of correction. The policy of prophylaxis of the habitual type of curvature is to prepare against the dangers involved during the period of rapid growth, which is between the ages of 3 and 5 and the prepuberty age. In early years, therefore, measures must be taken to develop the reserve force of the musculature of the back in maintaining the balance and symmetry of the body. A slight deficiency of the musculature, anemia, or a tendency to become fatigued easily must be noted at this age period and the proper measures taken. The condition of the upper respiratory passages with their accessory sinuses as well should be the subject of attention early.

It is necessary also that development of the thoracic muscles be carried on until the full standard of the respiratory excursion is reached. Children must develop the proper abdominal tone and must make satisfactory progress in weight. It should also be realized that it is not during puberty but before that most of the systematic infections occur that are apt to debilitate the body as a whole. In this period occur not only the contagious diseases, but also infections of the respiratory tract, etc. All these exhausting diseases necessitate a long period of reconstruction during which all possible aid must be given in the reestablishment of the organism to a normal state of resistance. So far as rickets as an underlying cause is concerned, the kyphotic preformation of scoliosis has already been described, but this is not the only effect which rickets has on the spine. Rickets not only produces a weakness of the musculature, but also a decided relaxation of the costovertebral articulations. Owing to this relaxation, the spine slumps down or collapses, with the result that a characteristic lateral curvature of the rachitic type develops. Curves in the spine which develop mainly between the ages of 11 and 14 years are also largely considered rachitic curves even if other signs of rickets are absent. It must be considered that rickets acts differently on the skeleton during different ages; while in the first year, there is general rachitic involvement of the skeleton, in later years there is involvement of the long bones, knock-knees and ankle valgus; still later, toward or during the period of puberty, the rapidly growing spine reacts to rickets by the formation of rachitic curves. It is still an open

question whether this may be an independent disease or a recrudescence of infantile rickets. At any rate, one must consider the weakened condition of the musculature of the back, probably of the body as a whole, together with a poor respiratory capacity and the relaxation of the abdominal tone, as the prescoliotic factors which lead to the development of rachitic scoliosis at the critical time of puberty. All therapeutic activity therefore must be directed toward the development of the normal resistance of the body as a whole and of the spine in particular. This means development of posture, of the thoracic musculature, of the breathing mechanism and of the abdominal tone.

CONCLUSION

Incipient scoliosis and the prescoliotic stage are two different conditions, both in point of quality and in point of occurrence. Incipient malposture or anteroposterior deformity and the predeformity stage are likewise two different conditions, both in point of quality and in point of occurrence.

Prophylaxis for scoliosis as well as for malposture when instituted at the first appearance of the definite deformity is undertaken too late; prophylaxis should begin at the time when the predisposing elements are recognized and before the first symptoms of actual deformity make their appearance. By understanding the nature of these predisposing elements, which are usually of a general character, it is possible to employ timely preventive measures. Because of the systemic nature of these predisposing causes, it seems that in the large majority of cases, it is the duty of the internist or the general practitioner rather than of the specialist to take the initiative in precautionary measures.

Pediatric Biographies

THOMAS PHAER
1510?-1560

JOHN RUHRÄH
BALTIMORE

One of the most interesting of the early English worthies was Thomas Phaer, physician, philosopher, poet and lawyer. In spite of the fact that he was not one of the intellectual giants of his day, he nevertheless had a place in law, literature and medicine. He was born in London, studied at Oxford and later in Lincoln's Inn. He first turned his hand to the law and wrote two practical books on the subject tending to popularize legal methods. This led to his appointment as a solicitor in the court of the Welsh Marches, and he settled at a house in Kilgerran Forest in Pembrokeshire, where he died in 1560. He gave his title as "Solicitor to Queen Mary, justice of the peace and *custos rotulorum* for the county of Pembroke." He had evidently practiced medicine as well, but did not obtain his degree until 1559, when he received his M.B. degree and permission to practice at Oxford. He received his doctorate a few months later.

Phaer had many friends among the literary lights of his day, one of them being George Ferrers, one of the editors of the "Mirror for Magistrates." Phaer had a penchant for popularizing knowledge and for writing verse. Besides his works on the law, he wrote numerous poems, including one on Owen Glendour; he nearly completed an English metrical version of Virgil's "Aeneid," which has many merits. His best known work in medicine is an English version of the "Regimen Sanitates Salerni," which he entitled, "The Regiment of Life." He also wrote a book on the plague.

His most important medical contribution was "The Boke of Children," which is the first book devoted to the diseases of children by an English author that I have been able to find. It was a popular work for over half a century and was reprinted over a half dozen times. Probably the last edition was published in 1596. In spite of this, it is a rare book sought by collectors. The text, of course, underwent some changes. In "Pediatrics of the Past," the text of the 1545 edition is reproduced in full. It is full of interest and nonsense, but is not without its merits if one takes into consideration the time in which it was written. In fact, today much is printed on pediatrics which four hundred years hence will sound just as nonsensical. Forty different diseases are considered in as many different chapters. There is some clinical observa-

tion, some theorizing, some opinions from previous writers and a rich, if somewhat hectic, therapy. An analysis of some of the remedial measures shows that they were sound and not as far from present day therapeutics as they seem to be at first sight. For example, the use of such applications as wine, myrrh and the like, that is, antiseptics and astringents, are used even at the present time in slightly modified forms. Then, too, the suggestion of using burnt hartshorne and claws of other animals for diarrhea, that is, animal charcoal, is a remedy highly lauded in a recent publication.

Two excerpts will serve to illustrate his style. The first, an example of early organotherapy which can more than be matched in present day literature, is as follows:

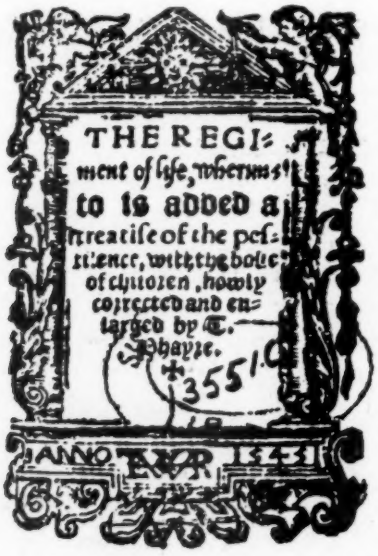


Fig. 1.—Title page of "The Regiment of Life," translation by Thomas Phaer.

OF PYSSING IN THE BED

Many times for debility of vertue retentive of the reines or bladder, as well olde mē as children are often-times annoyed, whan their urine issueth out either in theyr slepe or waking against theyr wylles, having no power to reteine it whan it cōmeth, therefore yf they will be holpē, fyrst they must avoid al fat meates, til ye vertue retentive be restored againe, and to use this pouder in their meates and drynkes.

Take the wesande [trachea] of a cocke, and plucke it, thā brenne it in pouder, and use of it twise or thryes a daye. The stones of an hedge-hogge poudred is of the same vertue.

Item the clawes of a goat, made in pouder droken, or eaten in pottage.

If the pacient be of age, it is good to make fyne plates of leade, with holes in them, and lette them lye often to the naked backe.

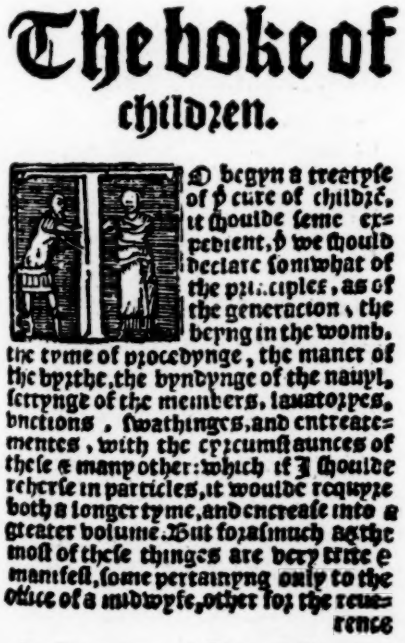
The second quotation shows a sounder therapy:

CHAFYNG OF THE SKYNNE

In the flankes, armeholes, & under the eares, it chaunceth often times that the skynne fretteth, ether by the childes own uryne, or for the defaute of washyng, or els by wrappyng and kepying to hote. Therefore in the begynnyng, ye shall annoint the places, with freshe, capons grece, then yf it wyll not heale, make an oyntment, and laye it on the place.

AN OYNTMENT FOR CHAFYNG AND GALLYNG

Take the roote of floure deluyce dryed, of redde roses dryed, galingale, and mastike, of eche a lyke quantytye, beate them into moste subtyle pouder: than with oyle of roses, or of lineseede, make a soft oyntment.


The boke of
childzen.

TO begyn a treetyse of þ cure of childzē, it thoulde seme expedient, þ we should declare sonwhat of the principles, as of the generacion, the beyng in the womb, the tyme of procedynge, the maner of the byrthe, the byndynge of the nauyl, sertynge of the members, lauatoryes, bnctions, swathinges, and entreatementes, with the circumstaunces of these & many other: which if I shoulde rehersse in particles, it would requyre both a longer tyme, and encrease into a greater volume. But forasmuch as the most of these thinges are very trite & manifest, some pertaynyng only to the office of a midwyfe, other for the reuerence

Fig. 2.—First page of Thomas Phaer's book.

Item the longes [lungs] of a wether dryed, and made in very fyne pouder, healeth al chafynges of the skinne, and in lyke maner the fragments of shomakers lether, brent and cast upon the place, in as fine pouder as is possible, hath the same effecte, whiche thing is also good for the galling or chafing of the fete, of whatsoever cause it commeth.

Item beane floure, barly floure, and the floure of fitches tempered with a lytle oyle of roses, maketh a soveraine ointment for the same entent.

If the chafinges be great, it is good to make a bath of holihocke, dyll, violets and lineseede with a little branne, than to washe the same places oftentymes, and lay upon the sore, some of the same things. The decoction of plantaine, bursa pastoris, horsetaile and knotgrasse, is exceadynge good to heale all chafynges of the skynne.

News and Comment

ADVANCEMENT FOR DR. CASPARIS

Dr. Horton Casparis has been made professor of pediatrics and head of the department of Vanderbilt University.

DR. ADLER MADE FELLOW AT MAYO FOUNDATION

Dr. Stuart W. Adler of Winona, Minn., has recently been made a Fellow in pediatrics at the Mayo Foundation.

APPOINTMENT OF DR. HETZEL AT YALE

Yale University announces the appointment of Dr. Joseph L. Hetzel, instructor and resident in pediatrics.

APPOINTMENT OF DR. STUART AT HARVARD

Harvard University announces the appointment of Harold Coe Stuart, assistant professor of child hygiene. Dr. Stuart has been a member of the department since 1922.

GIFT TO YALE

Mr. A. E. Fitkin, New York, has given $1,000,000 to Yale University, New Haven, to establish a foundation for the care of children, from the standpoints of curative and preventive medicine, the study of children's diseases, and the training of men for the achievement of these purposes.

APPOINTMENTS AT SYRACUSE

The Syracuse University announces the following appointments for instructors at the dispensary, department of pediatrics: Dr. Francis W. Rosenberger, Dr. Warren E. Saile and Dr. Michael J. Elwood.

Abstracts from Current Literature

Pathology, Bacteriology and Biochemistry

OBSERVATIONS ON THE ACTION OF ACETONE. NOAH MORRIS and S. GRAHAM, Arch. Dis. Childhood **2**:212, 1927.

Acetone injected intravenously in rabbits produced unconsciousness when the dose was more than 0.8 cc. per kilogram of body weight of 20 per cent solution. The urine was free from ketone bodies within twenty-four hours of the administration. There was a slight increase in blood sugar following injection. Dextrose accelerates the oxidation of acetone, and the value of alkali in the treatment of ketosis has long been known. Accordingly, injection of dextrose or alkali previous to the injection of acetone lessened the intensity of the acetone effect.

PETERMAN, Milwaukee.

THE CALCIUM AND PHOSPHORUS CONTENTS OF THE BLOOD SERUM OF INFANTS. O. ULMER and E. HILLENBERG, Arch. f. Kinderh. **83**:106 (Jan. 5) 1928.

In a study of the serum calcium and phosphorus in fifty-two children, it was found that the supposedly low values do not necessarily check with the clinical symptoms. In twelve infants who were free from rickets and tetany, the serum phosphorus was under 4 mg. in four cases. All of these infants, however, were somewhat undernourished. The majority of the determinations of serum calcium were under 10 mg., with the lowest 6.2 mg. In twenty-four cases of clinical rickets, also with definite roentgen-ray manifestations, twenty gave a serum phosphorus of less then 4 mg., with the lowest 1.6 mg. One case showed 6 mg. The lowest serum calcium was 6.2 mg., and the majority were between 8 and 10 mg. In sixteen children with definite spasmophilia, the serum phosphorus was under 4 mg. in twelve cases. The lowest was 1.8 mg., and the highest was 5 mg. The serum calcium was below 8 mg. in ten cases, the lowest being 4.8 mg., and the next 6.1 mg. The majority were between this figure and 8 mg. One case gave 12 mg. of serum calcium.

THE HEMOGLOBIN RESISTANCE IN YOUNG ANIMALS. H. BISCHOFF, Arch. f. Kinderh. **83**:161 (Feb. 17) 1928.

Bischoff tested the hemoglobin resistance of the blood of new-born animals with fourth normal sodium hydroxide. He found that guinea-pigs averaged 23.5 minims from birth to 12 weeks. The hemoglobin resistance of young rabbits increased from 19.9 minims at birth to 27.3 minims in twelve weeks. Kittens gave from 2 to 5 minims with no change, as did young rats at from 10 to 15 minims and chicks with 8 minims. Bischoff believes that this shows the presence of fetal hemoglobin.

THE EFFECT OF THE ULTRAVIOLET RAYS ON THE LEUKOCYTES IN CHILDREN. F. ILHAN, Arch. f. Kinderh. **83**:270 (May 23) 1928.

Erythema doses of ultraviolet light were given to eighteen children from 5 months to 5 years of age, and the blood picture studied at regular intervals. In healthy children there was a relative lymphocytosis at the expense of the neutrophils. In rachitic children there was an increase of the neutrophils at the expense of the lymphocytes.

SANFORD, Chicago.

EFFECT OF LOWERED AIR PRESSURE ON THE HEMOGLOBIN CONCENTRATION IN THE ERYTHROCYTES. L. DRASTSCH, Biochem. Ztschr. **195**:189 (April) 1928.

Drastsch kept guinea-pigs in an atmosphere of air at a pressure between 300 and 400 mm. of mercury. There was a greater percentage rise in the volume

of the red cells than in the hemoglobin content of the blood. The author feels that the immature red cells which enter the blood stream under such atmospheric conditions contain less hemoglobin than the mature cells. He also found some cells which were larger than normal.

BRAHDY, New York.

AN APPLICATION OF PREGL'S MICRO-ANALYSIS TO THE DETERMINATION OF FREE PHOSPHATES IN THE BLOOD. ERIK JORPES and HENNING MAGNUSSON, Acta Paediat. **7**:1 (Nov.) 1927.

The technical details are given of a gravimetric method for determining inorganic phosphates in 0.5 cc. of plasma. Using a little more than 2 cc. of blood obtained from puncture of the heel, the authors are able to make duplicate analyses which check to within 1 or 2 per cent. The article includes a discussion of the relationship of the various combinations in which phosphorus exists in the blood, and the precautions required for preventing the inclusion of organic phosphorus in the analysis for inorganic phosphates.

MCINTOSH, Baltimore.

Nutrition

CELIAC RICKETS. LEONARD PARSONS, Arch. Dis. Childhood **2**:198, 1927.

Changes in the bones are frequent in severe forms of celiac disease of long standing. These changes are rachitic in origin and are curable. Changes as shown by the roentgen ray in the bones of children past 7 years of age are: delay in the centers of ossification, osteoporosis, atrophy and sometimes fractures. The trabecular network is delicate. These changes are not found before the age of 7 years, because the celiac patient does not grow to any great extent. Rickets does not develop in infantile atrophy. When growth occurs to any extent, rickets develops. Blood chemistry in five cases showed low calcium and phosphorus. Tetany is often associated with celiac disease.

Treatment consists in ultraviolet irradiation, fat-free diet and administration of irradiated cholesterol. That the bony changes in celiac disease are rachitic in origin is shown by (1) roentgen-ray examination; (2) blood calcium and phosphorus; (3) clinical characteristics; (4) occurrence of tetany; (5) results of treatment by ultraviolet light and irradiated cholesterol.

PETERMAN, Milwaukee.

AN INVESTIGATION ON THE ANALYSIS OF HUMAN MILK. BERNARD MYERS, Brit. J. Child. Dis. **24**:249 (Oct.-Dec.) 1927.

In this study milk from 86 nursing mothers was analyzed and 184 separate analyses were made. Ninety per cent of the mothers were charity patients. In more than one third of the nursing mothers four consecutive test meals were made from the breasts alternately, and the average amount for each breast was recorded.

In one instance the fat percentage reached was 11.35 in the last third. The results of analyses of the first, second and third thirds show a higher percentage of fat in the third third. The average analysis in this series was: protein, 1.58 per cent; fat, 3.85 per cent; lactose, 6 per cent and the caloric value, 18.95.

As in the case of other investigators, the author found distinct variations from time to time and even during the course of a single day, this especially affecting the fat and protein content.

LANGMANN, New York.

ATHREPSIA. S. CORDEY, Rev. franç. de pediat. **4**:114, 1928.

Cordey insists that the essential feature of athrepsia is dehydration, in which the cells deprived of water are incapable of fixing it. The alimentation at first should be directed toward any food which will tend to fix water in the tissues. In this connection, barley water with its high salt content is valuable.

LESLIE, Evanston.

CONGENITAL RICKETS. W. GREIFF, Arch. f. Kinderh. **83**:23 (Jan. 5) 1928.

The serum phosphate of 100 new-born infants was studied. Twenty-three of these had a lowered serum phosphate. Of the fourteen children, including premature infants, with congenital skeletal anomalies, seven had lowered serum phosphate. There is therefore a relationship between congenital softness of the skull and a decrease of the serum phosphate. There is also a relationship between an abnormally low serum phosphate in the new-born and the subsequent appearance of clinical rickets. Of fourteen new-born infants with decreased serum phosphate, nine later had clinical rickets. In twenty-two new-born infants with normal phosphate content, only three developed rickets. Decreased phosphate content of the blood is much more frequent in premature than in full-term infants.

THE INFLUENCE OF COOKING ON THE SPECIFIC DYNAMIC ACTION OF FOOD. W. HILSINGER, Arch. f. Kinderh. **83**:193 (Feb. 17) 1928.

In three children, aged 9, 12 and 15, respectively, the specific dynamic action of 150 Gm. of meat and 500 cc. of milk, raw and cooked, was tested by means of numerous respiration experiments with the Zuntz-Geppert apparatus. The tests, which lasted twenty minutes, were repeated hourly for from five to ten hours after the ingestion of food. In most experiments cooked meat developed a somewhat higher specific dynamic action, which set in earlier than in the case of raw meat. The reason for this is that the disintegration of muscle fiber sheaths facilitates digestion and stimulates it by forming aromatic substances. In the milk experiments there was no evidence of a difference in the calory consumption curve between the raw and cooked liquid. The rise appearing after from one to two hours with milk as a "mixed food" was ascribed to its large carbohydrate content. The specific dynamic action decreases after from five to seven hours, and then rises generally without reaching the fasting level, owing to the latent rise in tonus, earlier action and the beginning of the metabolic processes of hunger. The respiratory quotient may also rise again, and this second rise may be taken as an indication that the question of constitutional differences in the examined, which would permit the outlining of certain types of curve for the specific dynamic action, might be the basis of anthropologic character types.

SANFORD, Chicago.

THE EFFECT OF ULTRAVIOLET LIGHT ON THE VITAMIN C CONTENT OF MILK. A. HOTTINGER, Klin. Wchnschr. **6**:1793, 1927.

Because of their known susceptibility to scurvy, the investigation was carried out on guinea-pigs. In addition to a standard oat-hay diet, 50 cc. of the milk to be tried was given daily to each of two guinea-pigs. If they showed signs of developing scurvy the amount of milk a day was increased to 80 cc., and then to 100 cc. for one of the animals while the other was allowed to continue on the 50 cc. quantity until death occurred. The controls, which did not receive milk, died with acute scurvy within from three to four weeks. Similar results were obtained in those animals receiving only 50 cc. of sterilized milks, sweetened or unsweetened Nestle's milk, dried milk Guigoz without sugar, Edelweiss milk, Ultraactina (irradiated Edelweiss milk) and nine months old Ravix (irradiated Guigoz milk). Those receiving up to 100 cc. of the foregoing milks were not protected from scurvy and died showing either chronic or acute scurvy. On the other hand, those receiving only 50 cc. of raw milk, dried Guigoz milk with sugar or fresh Ravix (irradiated Guigoz milk) showed only chronic or subacute scurvy, while those receiving 100 cc. of these milks recovered from their scurvy and continued in good condition. Thus, proper irradiation in no way diminished the vitamin C content of the dried Guigoz milk, while it greatly increased its anti-

rachitic property. Neither does slight cooking affect it. Aging, however, does affect it, as the nine months old Ravix had practically no protective action against scurvy. The dried Edelweiss milk, which does not have a protective action has a lower sugar and water content than the Ravix, and it is suggested that a certain amount of sugar and moisture in dried milk may be important for the preservation of the vitamine C content.

LESLIE, Evanston.

CLINICAL REPORT ON THE PROPHYLAXIS OF RICKETS. I. JUNDELL, Acta. Paediat. **7**:143 (Nov.) 1927.

Using pairs of twins, of which one served as a control, the author proved that therapy with cod liver oil begun before the age of 5 weeks effectually prevents rickets.

MCINTOSH, Baltimore.

EDEMATOUS DISEASE IN CHILDREN. F. D. ROUMIANTZEFF, J. Pediat. (Russian) **2**:3, 1927.

The author observed 100 cases of edematous disease in children during 1918-1922. In the anamnesis of the affected children, there were cases of enteritis, infectious diseases, such as recurrent fever, typhus, typhoid fever and measles and starvation, which in one case lasted for as long as three months. The premonitory period before the appearance of the edema was from six weeks to two months; in all cases the nutrition was poor. The clinical symptoms were gray, dry and flabby skin and pale mucous membranes. The patients moved little, preferred to lie down and complained of being cold.

The main symptom was the edema, which in some cases appeared first on the face and eyelids, as it does in patients with nephritis. More often the edema appeared in localized areas. In fewer cases exudation in the cavities was observed. In twenty-six the fluid was in the abdominal cavity and in four cases in the pericardium. The appetite was usually good; the patients complained constantly that they were hungry, and required large quantities of salt in their food. The stomach was normal; the stools were liquid in eighty-five cases; they had the character of enteritis, sometimes with blood and mucus and in some cases prolapse of the rectum. The abdomen was distended. The liver was enlarged in twelve cases, the spleen in ten cases. There were thirty-five cases of bronchitis, ten cases of tuberculosis and two cases of pleuritis, which did not show many changes in the heart and no bradycardia. Diminution of hemoglobin and a moderate leukocytosis with a lymphocytosis were found. Albumin and sugar were not found in the urine. Pathologic changes were not present in the kidneys in lethal cases. Fever was not found. Most of the patients had severe diarrhea which was difficult to check, but it diminished as soon as the patients were in a better condition of nutrition.

The author observed a high percentage of deaths: of the 100 patients, 53 died. The author agrees with Fisher that the cause of edema lies in the pathogenesis of the tissues. The last epidemic of edematous disease occurred in a disastrous period for Russia. Famine, cold, a series of epidemics and trying experiences of all kinds had undoubtedly changed the cells of the body and their functions. The famine manifested itself not only as lack of food but as a deficiency in the quality of food — lack of fats and animal albumin. The author considers the frequency of cases of tuberculosis among the lethal cases of edematous disease as an indication that the latter acts as an aggravating factor in latent cases of tuberculosis.

Treatment.—The most important thing is the improvement of those social conditions which are responsible for this disease. Thyroidin was useful in some cases, but that improvement of nutrition was the essential remedy was shown by the fact that as soon as the American Relief Administration began its activities to relieve the famine, the patients showed an improvement which could not be obtained with therapeutic agents.

THE USE OF CONCENTRATED FOOD IN YOUNG CHILDREN WITH DIARRHEA. V. G. BALABAN, J. Pediat. (Russian) **2**:31, 1927.

The question of concentrated foods at present occupies an important place in pediatric literature. The author observed forty patients; ten were from 7 to 12 months of age; twenty-five from 1 year to 2; four from 2 to 3 years, and 1, over 3 years of age.

CONCLUSIONS

1. Formerly, in children with diarrhea, the diet was incomplete because of the lack of fats, and caused dystrophia. It is necessary, therefore, to establish a diet which will meet two requirements: it must be a full diet and fats must be introduced in a form harmless to the diseased intestines.

2. A combination of albumin milk, and butter and flour mixtures, is satisfactory.

3. Especially favorable results are obtained in dystrophic children with diarrhea from 8 months to 3 or 4 years of age, since improvement in feeding stops the diarrhea.

4. In acute forms of intestinal disease the same regimen could be applied, except in patients with toxic manifestations.

5. The mixtures of fats are given after acute manifestations have subsided, and at first in small amounts. However, in cases having a tendency to become chronic, fats should be given regardless of the nature of the stool.

6. The indication for introducing food mixtures into the diet is the existence of dystrophia, or progressive loss in weight which is a symptom of approaching dystrophia.

7. In cases in which dystrophia has already developed, the same dietetic regimen may be applied.

SEVERAC, Philadelphia.

Prenatal Conditions

RECORDED CAUSES IN FIVE HUNDRED STILLBIRTHS IN NEW YORK CITY. LAURA W. NATHAN and GODIAS J. DROLET, New York State J. Med. **28**:78 (Jan. 15) 1928.

A study is made of reported causes of death in 498 stillbirths occurring in the district covered by the Bellevue-Yorkville Health Demonstration, in New York City. Only immediate causes of death are considered.

A stillbirth is defined as any nonviable product of conception delivered during gestation.

The results are best shown by the following table giving for comparison a U. S. Public Health report listing the causes of stillbirths in the 1924 Census Bureau report from selected sections in the Birth Registration Area:

Causes of Stillbirths	Bureau of the Census Study, per Cent	Bellevue-Yorkville Study, per Cent
All causes	100.0	100.0
Prolapse and compression of cord	9.1	6.8
Diseases of placenta and membranes	8.9	8.1
Difficult labor	8.6	7.0
Abortion, miscarriage and premature birth	8.2	13.7
Malpresentation	5.3	1.2
Albuminuria and other diseases incident to pregnancy	5.2	6.7*
Asphyxia of child (cause not stated)	4.1	15.1
Malformation	4.1	3.0
Traumatism and overwork	3.7	0.4
Syphilis	2.6	2.8
Death in utero	2.8	6.7
General diseases	3.1	...
Other specified causes	4.0	9.0
Causes not specified and unknown	30.2	19.5

* Toxemia and nephritis only.

AIKMAN, Rochester, N. Y.

Diseases of the New-Born

SOME OBSERVATIONS ON PIGMENT METABOLISM IN THE NEW-BORN. M. HINES ROBERTS, J. M. A. Georgia **17**:143, 1928.

In a study of the spinal fluid and blood serum of seventy-four new-born negro infants, the presence of bilirubin as shown by the positive indirect van den Bergh reaction was demonstrated. Quantitative estimates of this pigment by means of the icterus index showed its concentration in serum to be approximately 140 times as great as in the spinal fluid. The pigment concentration in both showed a steady rise to the fourth day of life followed by a gradual fall to normal by the eighth day, the relative concentration remaining consistently the same. Five cases of intracranial hemorrhage showed a marked relative pigment preponderance in the spinal fluid as compared with the serum.

MASHBURN, Atlanta.

MORPHINE AND MAGNESIUM SULPHATE INFILTRATIONS AND COLONIC ETHER INSTILLATIONS IN THIRTY-NINE CONSECUTIVE LABOR CASES. W. B. D. VAN AUKEN, New York State J. Med. **28**:84 (Jan. 1) 1928.

Intramuscular infiltrations of morphine and magnesium sulphate are given together with colonic instillations of oil ether. The method is found satisfactory from the obstetric standpoint. Results regarding the infant are reported in thirty-eight cases. Thirty-one gave spontaneous respirations and were otherwise normal. Two required a moderate amount of resuscitation, and five required from ten to twenty minute resuscitation. One of the latter died at the age of fourteen hours.

AIKMAN, Rochester, N. Y.

TRAUMA IN BIRTH INJURIES OF THE ARM. R. J. HARRENSTEIN, Ztschr. f. Geburtsh. u. Gynäk. **92**:476 (Jan.) 1928.

In twenty-four cases of paralysis of the arm, a separation of the proximal epiphysis of the humerus was found in two new-born infants and in another, aged 4 months. In all cases the affected arm was flaccid and inwardly rotated. In one case, sixteen days after delivery, a roentgenogram showed a fracture of the clavicle and a separation of the head of the humerus, which was indicated by the abnormal relation of the center of ossification of the epiphysis to the shaft of the bone. Beginning formation of callus could be seen. Five years later, motion at the shoulder joint was normal, and the extremity was 0.5 cm. shorter than the normal one. In another case, a swelling at the upper end of the arm was noticed a few days after delivery. Ten weeks later, roentgenograms showed formation of callus at the upper end of the humerus, but motion at the shoulder joint was almost normal. The center of ossification was not visible. Three and a half years later, the arm and shoulder were normal. The third patient, who was seen four months after delivery, had contractures of the internal rotators of the arm. Roentgenograms showed displacement of the proximal epiphyseal center of ossification in relation to the shaft of the humerus. The arm was placed in a plaster cast in abduction and external rotation. Three and a half years later, there was slight limitation of motion at the shoulder and the extremity was 0.5 cm. shorter than the normal one. Roentgenograms showed the epiphysis retarded in development, but the shaft was normal.

In eight of twelve patients examined roentgenologically in the first month of life, the ossification center of the proximal epiphysis of the humerus could be seen on both sides, and in one case on one side.

BRAHDY, New York.

CONGENITAL GOITER. EMIL WIELAND, Schweiz. med. Wchnschr. **57**:850, 1927.

Congenital goiter is not rare in the neighborhood of Basel, Switzerland. It is recognized by: (1) a tendency on the part of the infant to keep the head thrown backward; (2) an inspiratory stridor which tends to disappear in sleep and during

complete rest, and is exaggerated on crying; (3) hoarseness; (4) difficult and slow nursing; (5) striking swelling of the veins of the head and neck with pressure or crying and a generally bluish color of the lips, cheeks and brow, and finally (6) the palpation of an enlarged thyroid gland. The condition reacts promptly to iodine, which is rubbed into the skin locally in the form of potassium iodide salve.

LESLIE, Evanston.

Acute Infections

THE EFFECTS OF ANTITOXIN ON THE LEUKOCYTES IN DIPHTHERIA. R. F. SOWELL, M. Clin. N. Amer. **11**:1293 (March) 1928.

Thirty-three selected cases of diphtheria were studied to determine the effects of antitoxin on the leukocytes. In 42 per cent, preceding definite leukocytosis was increased after the administration of antitoxin. An increase in the count in patients with a slight leukocytosis was noted in 12 per cent. In 40 per cent with definite leukocytosis, there was a decrease in the count after the administration of antitoxin. In two cases (6 per cent) in which there was a leukopenia, an increase in the count occurred.

Antitoxin apparently did not materially affect the differential count, although in four cases a definite eosinophilia occurred after its administration. In many cases the neutrophils seemed to take the stain more readily after serum was given. The size of the dose did not materially affect the total white count or the differential count.

SMITH, Ogden, Utah.

ACTIVE IMMUNIZATION IN SCARLET FEVER. H. BUSCHMANN, Arch. f. Kinderh. **83**:33 (Jan. 5) 1928.

It was found that a protective inoculation against scarlet fever with the Dick toxin, whether given subcutaneously or intracutaneously, exercises an influence on the leukocyte picture. This change appears in the neutrophil eosinophils and lymphocytes, which are increased beyond the limits of physiologic fluctuation. To protect against scarlet fever by means of inoculation, it is therefore necessary to give the serum in such doses as to cause this change in the blood picture.

EXPERIENCES WITH WHOOPING COUGH. G. ABRAHAM, Arch. f. Kinderh. **83**:185 (Feb. 17) 1928.

Abraham tried three proprietary preparations to immunize and protect from pertussis. Some prophylactic immunization was indicated in two of the preparations containing mixed organisms as a vaccine. They did not have a particular effect on the course of the disease. The third remedy, which contained a mixture of the usual remedies used in pertussis, also did not have a particular effect on the course of the disease.

GANGRENOUS ULCERS OF CHICKENPOX COMPLICATING MEASLES. J. KONDO, Arch. f. Kinderh. **83**:190 (Feb. 17) 1928.

Kondo reports a case from Japan of a child, aged 18 months, with typical measles. Six days after the appearance of the measles rash an eruption of chickenpox appeared. On the back several of these vesicles coalesced to make deep gangrenous ulcers which crusted over and then broke down. The child recovered completely.

HAS INFLUENZA ANY INFLUENCE IN THE SPREAD OF OTHER INFECTIOUS DISEASES? Z. VON BARABÁS, Arch. f. Kinderh. **83**:256 (March 23) 1928.

In a review of the literature of the epidemics of influenza, the author concludes that while many acute and chronic infections are aggravated by this disease, there is no particular evidence that influenza aids in the spread of these conditions.

SANFORD, Chicago.

EXPERIENCES WITH THE DICK TEST IN PATIENTS WITH SCARLET FEVER. L. ABRAMSON, Acta Paediat. **7**:138 (Nov.) 1927.

In a series of 182 cases of scarlet fever, most of them mild and with only one death, the Dick test yielded irregular results. A change from an originally positive reaction to a subsequently negative one was found in 42 per cent, the change occurring sometimes in the second or third week, but often not before the eighth or even the twelfth week. In 27 per cent the test remained positive as long as the patient remained in the hospital, and in 22 per cent it remained negative throughout. The change from positive to negative occurred more often in older patients. Persistently negative reactions were not found in children from 1 to 3 years of age. Tests were made once a week. There were seven patients whose tests, originally negative, later became positive; and in three of them this change was synchronous with the occurrence of some complication of the disease.

McINTOSH, Baltimore.

PERCUTANEOUS GONOCOCCUS INFECTION IN AN INFANT AGED FOUR WEEKS. A. DEUBER, Schweiz. med. Wchnschr. **57**:156, 1927.

A boy, aged 4 weeks, was brought to the hospital because of whooping cough. On admission, a superficial abrasion was noted on the skin over the left external malleolus. The following day the area had become red and swollen, and a little later fluctuation was noted. Intracellular gram-negative diplococci were found in the fluid obtained from the abscess. Following this, abscesses developed on the right hand, in the right axilla and over the right scapula, all yielding the same organism. These were treated with 1 per cent strong silver protein. Except for a pustular infection with hemolytic staphylococci, the infant made an uneventful recovery. A careful search was made for gonococci in all other portals of entry without a trace of any such infection being found. An intra-uterine infection is highly improbable, because of the interim following birth in which there was no evidence of infection. The author feels that there is no doubt that the infection with the gonococci took place through the abrasion on the left foot, which may have been a slight burn from a hot water bag. The father and mother and also the nurse had gonorrheal infections.

LESLIE, Evanston.

VACCINOTHERAPY IN CHILDREN WITH TYPHOID FEVER. K. SHWARTZACH, J. Pediat. (Russian) **2**:15, 1927.

While European and American literature contains many publications on vaccinotherapy, so far nothing has been published on the subject in Russia, and the author therefore decided to publish her own observations.

Vaccinotherapy was applied to twenty-eight children; two of them had other infectious diseases — pneumonia catarrhalis and influenza. The author did not observe any untoward effect of the vaccination. The vaccine was prepared in the Bacteriological Institute of Kieff by the method of Kolle-Pfeiffer; each cubic centimeter of the vaccine contained 500,000 killed bacteria. After one or two days of control, the vaccine was injected below the angle of the scapula; in one case in the inner part of the hip and in another case in the region of the abdomen. A local reaction was not observed. At first the author used small doses for fear of reactions (from 0.1 to 0.3 cc.); she then increased the doses to from 0.5 to 1 cc., the number of injections being from 2 to 6 with an intermission of from one to three days. After the injection the temperature usually rose after two hours from 0.5 to 2 degrees, going down the next day.

CONCLUSIONS

1. Improvement in the general condition occurred after the second or third day.

2. The temperature fell after the second or third injection.

3. There was a decrease in the duration of the illness, on the average, to eighteen days; in untreated patients, the duration of the illness was twenty-four days.

4. Absence of untoward reactions was found even in cases in which the vaccination was applied in other infectious diseases. The author suggests that observations on vaccinotherapy should be made with more material.

PRENATAL MALARIA. R. S. RAPOPORT, J. Pediat. (Russian) **2**:61, 1927.

In 1922-1924, when a severe epidemic of malaria spread throughout Russia and especially in Moscow, cases of malaria were observed in children a few months old and born of malarial mothers.

The author observed in the Ambulatorium of the Roussakovsky Children's Hospital, two cases of malaria in children 2 and 3 months old, born of malarial mothers. These two cases were interesting because the malaria appeared in children with congenital syphilis.

In the first case, the child entered the hospital with high temperature, with remissions in the morning characteristic of malaria; a large number of plasmodia were found in the blood. The namnesis of the mother showed that malaria appeared during the fourth month of pregnancy. The Wassermann reaction of both the mother and child was ++++. The child's liver and spleen were much enlarged.

In the second case, a child, aged 3 months, according to its mother had fever on the second day after birth. The Wassermann reaction was ++++. The blood contained a large amount of *Plasmodia tertiana*. The liver and spleen were large. The child was treated with neoarsphenamine, and the plasmodia disappeared from the blood.

The author thinks it possible that the pathologic changes in the placenta due to syphilis facilitate the transmission of malaria from mother to child.

The author concludes: 1. Prenatal malaria is recognized by most authors. The conclusive evidence consists in the cases in which plasmodia are found in the blood of a new-born child.

2. However, malaria is not always transmitted from the mother to the child. Most authors think that the normal placenta is a nonpassable filter for the plasmodium.

3. The pathologic change in the placenta facilitates the passage of the plasmodia from the mother to the child.

4. The mechanism of the transmission and its frequency are questions for further observations.

5. It is possible that congenital syphilis is one of the factors of the transmission (as in the author's cases).

6. It is necessary to observe the children of a malarial mother from the first days of life; the blood should be examined as soon as possible, as well as the pathologic structure of the placenta.

SEVERAC, Philadelphia.

Chronic Infections

LATE HEREDITARY SYPHILIS WITH LUNG COMPLICATIONS. REPORT OF TWO CASES. ARCHIBALD D. SMITH, Am. J. Syph. **12**:177 (April) 1928.

The author reports two cases with pulmonary involvement in children with hereditary syphilis. The x-ray and physical manifestations were much like those of pneumonia. The older patient, a child, aged 12 years, had a productive cough, with purulent nontuberculous sputum. The younger patient, a child, aged 5 years, had a nonproductive cough. Both were poorly nourished and in poor general condition. Both patients showed an elevation in temperature after the administration of arsphenamine. The roentgenograms showed a marked pulmonary involvement.

SYPHILIS AND PREGNANCY. SOME RESULTS OBTAINED FROM TREATMENT. AN ANALYSIS OF TWO HUNDRED AND FIFTY CASES. J. R. MCCORD, Am. J. Syph. **12**:181 (April) 1928.

The author reports 250 cases of maternal syphilis in which the patients have been treated during pregnancy. The plan is to prevent syphilis in the infant rather than cure syphilis in the mother. The treatment consists of 0.45 Gm. of neoarsphenamine and an inunction of mercury weekly from the time the patient comes under observation until the infant is born. The placenta was studied in 192 cases; x-ray examination of the bones in ninety-five, and maternal blood Wassermann tests were taken in 184 instances.

In this group, 12.5 per cent examined by x-ray showed evidence of syphilis, but with one exception, these all occurred in children whose mothers had had less than three treatments.

A serologic study was made of 229 infants. It was positive in 42, an incidence of 18.3 per cent. Of these, 36 had had less than 6 treatments; in the other 6, the number of treatments ranged from 7 to 15.

The placenta was studied in 192 instances. In 79 of these the results were negative; in 55, they were positive, and 59 showed evidence of having been influenced by treatment.

The maternal Wassermann test was repeated in 173 instances. Of these, 95 had been reduced from strongly positive to negative; 78 remained strongly positive, but 54 of these patients had received less than 5 treatments, and in no case was the Wassermann reaction positive in a patient who had received 13 or more treatments.

If the placenta shows syphilis, the infant is syphilitic, but the infant may be infected when the placenta does not show any change. Treatment should be begun early in all cases. The author found that syphilis with pregnancy does not increase the maternal hazard.

SYPHILIS OF THE OSSEOUS SYSTEM. A. H. GALVIN, Am. J. Syph. **12**:187 (April) 1928.

The author finds that the Wassermann test is less constantly positive in osseus syphilis than in other forms of the disease, but believes that the luetin test is of considerable value. Syphilis of the bone is a constructive process. The lesion is typical, and a diagnosis may be made from the plates alone.

The lesions of the bones may be classified roughly as follows: (*a*) Tuberculosis and maligant conditions cast shadows which are destructive. (*b*) Osteomyelitis and syphilis cast shadows constructive in character. (*c*) Lesions of the bones that are constructive in nature are usually benign. (*d*) Lesions of the bones that are destructive in nature are usually malignant.

In the differential diagnosis, the following conditions must be borne in mind: tuberculosis, chronic pyogenic osteomyelitis, sarcoma, carcinoma and rachitis.

The treatment is that used in primary and secondary syphilis, except that it need not be so intensive.

CONGENITAL SYPHILIS OF THE TESTICLES. WITH REPORT OF TWELVE AUTOPSIED CASES. WILLIAM C. MENNINGER, Am. J. Syph. **12**:221 (April) 1928.

Congenital syphilis of the testicle was first described by Gasselin in 1858-1859, the patient being an infant 10 months of age. The pathologic condition was first described by Depres. The author reviews the wide difference of opinion held as to the frequency of this involvement, i. e., Barker (1917) describes it as extremely rare; Herxheimer (1908), frequently seen; Warthin (1916), testes swarm with spirochetes even when histologic changes are not noted.

In the experience of the author the majority of cases do not show enlargement of the organ; in many the organ is smaller than normal. Atrophy may follow

the enlargement occasionally, the end-stage being almost complete atrophy. In some instances there appears to be an aphasia rather than an atrophy. The surface is sometimes nodular, although it is usually smooth.

Hydrocele is present in a certain number of cases; it is usually unilateral but may be bilateral. However, Still states that it is seldom seen.

The author did not find macroscopic gummas in his cases, but these are reported by other authors. The globe is usually affected alone, but occasionally the epididymis is also involved.

As to the clinical course the author states that the disease is probably usually present at birth and goes through life undiagnosed. When swelling occurs it usually does so between the third and tenth month and diminishes during the second year. It has been noted, however, as late as the fifteenth year. In all of the author's cases there were one or more gross syphilitic lesions in addition to the orchitis.

The indirect consequences are aplasia, sclerotic atrophy and sarcoceles, the latter comparable to those of acquired syphilis, with either of the former coming on at an early age; infantilism results. This infantilism does not differ in any way from that produced by other causes. It may be general or it may be limited to the sexual organs.

McBRIDE, Sioux City, Iowa.

INNATE RESISTANCE TO TUBERCULOSIS. CHARLES T. RYDER, Am. Rev. Tuberc. **17**:103 (Feb.) 1928.

The great majority of people have a high degree of resistance to all common infectious diseases, including tuberculosis. This resistance is an innate or inherited characteristic, and it is manifest on first infection, though it is possible that it is not always fully developed at birth. A race long exposed to a disease has a much higher innate resistance to it than a race newly exposed. In the case of endemic diseases, or "universal viruses," to which practically all persons are exposed, first infections usually take place in the first years of life. The great majority combat these infections successfully, because of their innate resistance. In an endemic disease in which recovery is followed by a high degree of immunity, practically all deaths occur in infancy and childhood, the period of first infection. Diseases which are not marked by increase of immunity show high death rates in maturity and old age. In the case of tuberculosis, first infection in childhood does not produce illness, as a rule, and is attended by a low death rate. This resistance on first encounter with the tubercle bacillus must be an inherited trait. After this period, the death rate rises rapidly and maintains a high level throughout life. This indicates that natural first infection with the tubercle bacillus, though well resisted, is not followed by any effective increase in immunity, but rather the reverse. Especially in pulmonary tuberculosis, the altered tissue reaction following first infection seems to favor the development of disseminated ulcerative phthisis.

X-RAY AND CLINICAL DIAGNOSIS OF TUBERCULOSIS IN CHILDREN. HENRY D. CHADWICK, Am. Rev. Tuberc. **17**:318 (April) 1928.

Hilum tuberculosis, or the juvenile type of tuberculosis, is the form of the disease which follows a first infection of a child's lung with the tubercle bacillus. It manifests itself by a small, circumscribed primary lesion in the pulmonary parenchyma, accompanied by involvement of the tracheobronchial lymph nodes which drain the area of the primary infection. Even though symptoms of active disease are absent, the so-called latent hilum tuberculosis, because of the age of the child, such lesions must be comparatively recent and contain living tubercle bacilli. The diagnosis of juvenile tuberculosis rests on the following factors listed in the order of their importance: roentgenologic evidence of calcified tracheobronchial lymph nodes in the lung; positive tuberculin tests; history of exposure to case of open tuberculosis, and physical signs and symptoms.

A diagnosis of juvenile tuberculosis can be made only from a study of the roentgenogram. Slight changes in density in the shadows at the hilum are not significant. Tracheobronchial lymph nodes and pulmonary nodules which show evidence of calcification are tuberculous. In the case of large homogeneous shadows, time and serial films taken at intervals of several months are necessary to determine the nature of the infection. These patients should, however, be considered as suspects until a positive diagnosis is possible. Small circular or oval densities due to blood vessels caught in the same axis as the ray may simulate calcified areas. They are often found near the hilum in the fifth interspace, and are often seen close to a bronchus in cross-section outline.

In children, a positive tuberculin skin test indicates the presence of living tubercle bacilli. The intracutaneous test is used in the more delicate children and is the method of choice. In the Massachusetts State Clinics, 48 per cent of the children aged 6 years said to be contacts were reactors, and only 15 per cent of the non-contacts were of the same age.

There are few physical signs indicative of juvenile tuberculosis. None are pathognomic. Auscultation and percussion are important only as they may determine the absence or presence of other disease conditions. Pleurisy with effusion should be considered among the physical signs of juvenile tuberculosis. Such symptoms as undue fatigue, nervous irritability, frequent colds or fever are not important factors in diagnosis, but are important as an index of the activity of the disease.

SMITH, Ogden, Utah.

POINTING TUBERCULOUS EMPYEMA AND TUBERCULOUS RIB. W. M. FELDMAN, Proc. Roy. Soc. Med. **21**:224 (Dec.) 1927.

In a child, aged 8 years, fourteen days before admission a lump on the right side of the chest was noticed, but pain had been present across the chest posteriorly for several weeks with slight cough. Examination revealed a fluctuating swelling over the third and fourth right costal spaces, internal to the nipple line. Roentgen-ray examination showed interlobar empyema. Aspiration was performed the next day, March 24, 1927, when thick pus containing scanty tubercle bacilli was withdrawn. On March 29, resection of the rib was performed, and much pus was evacuated. On May 12, the wound was completely healed and the child was discharged. On June 4, the child was gaining in weight but was still having some pyrexia. The child was readmitted to the hospital on July 7, with swelling in the region of the tenth rib on the right side but no involvement of the skin. On aspiration, 4 cc. of thick pus containing many pus cells but no tubercle bacilli was withdrawn. Resection of the axillary portion of the rib was performed. The rib was diseased and showed a sequestrum.

WILLIAMSON, New Orleans.

A STUDY OF TUBERCULOSIS IN INFANTS. M. A. ASSERON, Tubercle **60**:323 (April) 1928.

For the purpose of obtaining recent figures on the incidence of tuberculous infection among infants in New York City, intradermal tests were made on 1,656 infants attending clinics and health stations, and hospital records of 4,003 infants under treatment during a period of five years were studied. Positive tests were obtained as follows: in infants in hospitals, 11.4 per cent; in clinics, 4.5 per cent; at health stations, 1.3 per cent. The incidence of infection among infants of various races and nationalities was found to be similar. However, the ability to resist infection corresponded closely to the race or nationality to which they belonged. Follow up study of the positive reactors showed that the infant's resistance to tuberculous infection was higher than it was formerly believed to be, but that his resistance to tuberculous disease was relatively low.

SMITH, Ogden, Utah.

THE FILTRABLE VIRUS OF TUBERCULOSIS. SAINT-GIRONS, Nourrisson **15**:287 (Sept.) 1927.

It has been held for many years that cases of hereditary tuberculosis do not exist; that tuberculosis in early infancy is always due to postnatal contagion. Now it becomes necessary to modify this view somewhat. Several French investigators have shown conclusively that if tuberculous virus is passed through a Chamberland filter and the filtrate is inoculated into guinea-pigs, tubercle bacilli can subsequently be found in glands of these animals. Evidence is also presented that such virus can pass through the human placenta and give rise to tuberculosis of the mesenteric glands in the infant. In nine infants or fetuses who after birth or extraction had not had contact with their tuberculous mothers, Calmette, Valtis and Lacomme were able to find tubercle bacilli in three by direct examination and in all to prove the presence of tuberculous infection by inoculations into guinea-pigs. This hereditary virus varies a good deal in its virulence and may be demonstrable in the offspring only by a transient tuberculin reaction. These cases of intra-uterine contagion must be regarded as exceptional, and the author still insists that the great majority of infants with tuberculous mothers are born without taint, and if promptly separated from their infected mothers may be expected to develop normally; also that postnatal contagion remains the most important factor in tuberculosis of young infants.

McCLELLAND, Cleveland.

TUBERCULOSIS AND HEREDITY. L. BERNARD, Presse méd. **36**:369 (March 24) 1928.

After an exhaustive study of the subject of the hereditary factor in tuberculosis, Barnard concludes that both old and recent observations show that heredity is not a factor in the propagation of tuberculosis. The hereditary transmission of the bacillus occurs in only a small number of cases. The great diffusion of the disease is due to contagion, and this fact is of the greatest importance in outlining prophylaxis.

SANFORD, Chicago.

TREATMENT OF EXTERNAL TUBERCULOSIS BY METHYLIC ANTIGEN. A. HENRY, Rev. de la tuberc. **9**:40 (Feb.) 1928.

Henry reports a series of twenty cases of tuberculous glands, ulcers, fistulas, and one case each of lupus and tuberculous peritonitis with ascites in which the patients were treated by injections of the methylic antigen, with uniformly successful results. Except in cases in which there was pulmonary involvement, the general health of the patients rapidly improved, nonsuppurating glands became fibrous nodules, and suppurating glands, after evacuation of pus, soon cicatrized. Fistulas and ulcers healed without intervention. One case of lupus, in which skin grafting had previously been performed with extension of the disease to the grafted skin, was completely healed after thirty injections. In the case of peritoneal tuberculosis, the ascites had disappeared after the twentieth injection.

The methylic antigen was developed in the Pasteur Institute by L. Negre and A. Boquet. It has been determined that the acetone soluble fatty and waxy portions of the tubercle bacillus have the property of accelerating the extension of the tuberculous process in all organs. On the contrary, the phospholipoids extracted by methyl alcohol have a decided antigenic action against this infection. The methylic antigen is prepared by first defatting the bacilli with acetone, and then treating with methyl alcohol, which is later driven off by distillation in vacuo. The residue is emulsified in an equal quantity of physiologic sodium chloride solution. Two strengths of the antigen are used, the pure and a one-tenth solution. Treatment is commenced by the injection of 0.25 cc. of the dilute antigen twice a week. Four injections of this strength are made before the dose is increased to 0.5 cc. This is followed in like manner by doses of 0.75 and 1 cc. Next, the pure antigen is given in similar doseage and progression. The dose is

reduced if a rise in temperature occurs. The injections are innocuous if proper dosage and progression are observed. The author has employed the antigen in forty cases and has not observed any accidents from its use. After several injections, slight induration and redness occur at the site of inoculation, which disappear spontaneously.

EXAMINATION OF THE INFANT'S STOOL FOR THE BACILLUS OF KOCH. DENIS SZULE, Rev. de la tuberc. **9**:49 (Feb.) 1928.

The author found tubercle bacilli in the stools of all of his patients with ulcerating tuberculosis, while in those with latent disease or with "tuberculose ganglio-pulmonaire," he found uniformly negative results. He feels that it is safe to conclude that the disease is noncontagious in infants in whom the cutireaction only is positive, and who do not show clinical or roentgenologic signs of the disease.

SMITH, Ogden, Utah.

CONGENITAL SYPHILIS. R. FISCHL, B. EPSTEIN and F. BREINL, Arch. f. Kinderh. **83**:44 (Jan. 5) 1928.

Rabbits could not be infected by syphilitic material rubbed on scarified mucous membrane, but if the material was placed in the female genital organs the male could be infected. An infected male, however, did not cause the mother to have syphilitic offspring. A fourth group was infected by way of the cornea. An infection could also be caused by the injection of syphilitic material into the blood stream, provided the material was obtained from that species of animal to be infected. In this respect it was found impossible to infect guinea-pigs with syphilitic material from rabbits, and their young appeared to be normal when born.

THE PRESENCE OF SPIROCHAETA PALLIDA IN CONJUNCTIVAL AND NASAL SECRETIONS OF CONGENITALLY SYPHILITIC INFANTS. F. WEISS, Arch. f. Kinderh. **83**:68 (Jan. 5) 1928.

In twenty infants under 1 month of age without physical signs of syphilis and only a positive Wassermann reaction in the mother as a diagnostic aid, spirochetes were found in the conjunctival or nasal secretions. In forty-two infants with syphilitic manifestations, spirochetes were found in the nasal secretions in eleven cases — five times in the conjunctival secretions, and twelve times in both, making a total of twenty-eight cases. The authors believe that the conjunctiva is specifically irritated by the organism, and that the chances of finding the organism is equal in younger or older infants. These observations should prove a valuable diagnostic aid in the differentiation of exanthems with conjunctivitis, and a specific diagnostic aid of syphilitic infection.

SANFORD, Chicago.

NONPATHOGENICITY OF CALMETTE'S B.C.G. R. KRAUS, Wien. klin. Wchnschr. **41**:441 (March 29) 1928.

Kraus summarizes the results of his animal experiments made to determine the pathogenicity of Calmette's B.C.G. strain of bovine tubercle bacilli for preventive vaccination of children against tuberculosis. Only 2 out of 100 guinea-pigs injected intraperitoneally with B.C.G. died. Omental abscesses containing tubercle bacilli were demonstrable in the fatal cases, but cultures and animal inoculations with material from the lesions proved negative. The surviving guinea-pigs gained weight normally, as did also several rabbits similarly inoculated with B.C.G. many months previously. Although guinea-pigs killed six weeks following inoculation with B.C.G. showed typical tuberculous lesions in the omentum, spleen and other organs, those on whom autopsies were performed eighteen months after injection did not display signs of tuberculosis.

The author does not agree with Korschum or with Petroff, who assert that the B.C.G. strain may acquire increased virulence by successive passages through animals. He regards it as a fixed virus. Noting the fact that infants inoculated with B. C. G. are only slightly reactive to tuberculin, Kraus made experiments on the tuberculin reactivity of guinea-pigs inoculated with B.C.G. He found that animals injected peritoneally with B.C.G. survived subsequent intraperitoneal introduction of human or bovine tuberculin, while controls that had not been inoculated with virulent strains of tubercle bacilli died following administration of tuberculin.

The author concludes that B.C.G. is nonpathogenic. He reiterates, however, that further autopsies on vaccinated infants who have died from intercurrent disease are advisable before the product is finally judged to be safe for general clinical use.

OLMSTED, Seattle.

CRITIQUE OF CALMETTE'S ANTITUBERCULOSIS VACCINATION. A. WALLGREN, Acta Paediat. **7**:120 (Nov.) 1927.

Wallgren presents destructive criticism of Calmette's reports of the results obtained with the use of B.C.G.

MCINTOSH, Baltimore.

HEMOPTYSIS AND HEMORRHAGES IN TUBERCULOSIS OF CHILDREN. N. B. ROSENTHAL-NISSNEVITCH, J. Pediat. (Russian) **2**:41, 1927.

The majority of authors consider hemoptysis and hemorrhages in tuberculosis of children as rare complications, especially hemorrhages in the lungs.

The material for the author's work consisted of 456 patients who had passed through the First Moscow Tuberculosis Hospital for Children since it was founded. Among the 456 patients, 25 had hemoptysis and 6 hemorrhages, which represents 5.5 per cent of hemoptysis and 1.3 per cent of hemorrhages. In the 25 cases of hemoptysis, 16 occurred in the hospital, and 9 previous to the patient's coming to the hospital. Out of 219 girls observed, hemoptysis occurred in 18, which is 8.2 per cent; in boys, the percentage is lower—out of 236, 7 had hemoptysis, which is 3 per cent.

CONCLUSIONS

1. Hemoptysis and hemorrhages, especially, seldom occur in children, and in most cases those affected are older children.

2. Girls have hemoptysis more often than boys.

3. Hemoptysis and hemorrhages are observed in children whose lungs are deeply affected, in most cases with caverns in the upper lobes.

4. The appearance of hemoptysis does not influence the prognosis; repeated hemorrhages from the lungs with large pathologic changes lead to a lethal end. Hemorrhages in children with slight changes in the lungs have better prognosis.

5. Hemoptysis and hemorrhages usually appear repeatedly, at different intervals. In hemoptysis, the amount of blood expectorated is small; in hemorrhages the loss of blood is considerable, sometimes more than 2 glassfuls.

6. Children who have hemorrhages usually show many other diseases in the anamnesis; all of them have had measles, whooping cough and pneumonia.

SEVERAC, Philadelphia.

Internal Diseases

A CLINICAL PATHOLOGICAL AND BIOCHEMICAL STUDY OF AMYLOID NEPHROSIS. G. C. LINDER, J. MAXWELL and F. H. K. GREEN, Arch. Dis. Childhood **2**:220, 1927.

A clinical history is given of a boy, aged 13 years, who had had recurring edema during the preceding nine years. Edema first occurred a few weeks after bilateral mastoidectomy at the age of 4 years. One mastoid wound continued

to discharge from time to time. Hypertension was not present. The urine showed large amounts of protein. In the latter months of the disease, the serum cholesterol was increased; the balance of acid and base was closely followed and revealed the changes which take place in the terminal stages of chronic nephritis. At autopsy the kidneys were reduced in size. Amyloid degeneration with a fair amount of fatty degeneration was found. Amyloid nephrosis was perhaps due to persistent aural sepsis.

PETERMAN, Milwaukee.

CYANOSIS IN INFANTS FROM NITROBENZINE. A. M. STEVENS, J. A. M. A. **90**: 116 (Jan. 14) 1927.

A report is given of twin infants who developed severe cyanosis, with rapid pulse and respiration rates. The symptoms were due to inhalation of the fumes of a toilet deodorant which contained nitrobenzine erroneously used as an insecticide. The infants survived and are now apparently normal.

DIPHTHERIA PROPHYLAXIS AMONG ASTHMATIC PATIENTS. GEORGE L. WALDBORT, J. A. M. A. **90**:290 (Jan. 28) 1928.

The increased popularity of diphtheria immunization brings up the question of inoculating persons with asthma. From a theoretical point of view, caution should be recommended in the administration of toxin-antitoxin to asthmatic patients. However, practical experience, as far as evidenced by the literature, does not seem to bear out this consideration. The author noted that six children who were free from asthmatic symptoms for several months had recurrences of attacks coincidentaly with the administration of toxin-antitoxin. In two other children the inoculations were followed by initial asthmatic attacks. The asthmatic attacks were severe and not as easily controlled as usual. The skin tests were positive for horse serum; in all eosinophilia was present, and in seven the eosinophilia was higher after inoculation. It may be possible, by giving small desensitizing doses or serum, to prevent untoward symptoms from diphtheria prophylaxis in allgeric patients.

BONAR, Salt Lake City.

SICKLE-CELL ANEMIA. J. HOLMES SMITH, JR., M. Clin. N. Amer. **11**:1171 (March) 1928.

Smith says that sickle cell anemia is rarely recognized in New Orleans. He reports the case of a mulatto girl who first came under observation at the age of 11 years, and whose chief complaint was red urine which stained her clothing. This symptom had been of irregular occurrence since the age of 2 years. She had also experienced at various times pain in the abdomen, particularly on the right side, unaccompanied by nausea or vomiting, weakness and pains in the muscles and joints. These symptoms bore a constant relationship to the appearance of the red urine. When the urine was pale, she usually felt well. Positive physical signs were an icteric tint to the sclera and tenderness over the right side of the abdomen, especially in the region of the gallbladder. The spleen had not been enlarged, but there had possibly been a slight enlargement of the liver. Laboratory examinations showed slight anemia, bile pigment in the blood and a strongly positive urobilin reaction in the urine. A tentative diagnosis of congenital hemolytic jaundice was made, as sickle cells were not recognized in the blood. About three years after the first examination, on recurrence of the symptoms, examination of the blood showed: hemoglobin, 60 per cent; red cells, 2,705,000 and leukocytes, 6,750. Marked anisocytosis and poikilocytosis, a few normoblasts and a few red cells of the sickle-cell variety were present. On subsequent examinations, sickle-cell changes were found in from 5 to 10 per cent of the total erythrocytes, varying only slightly with exacerbation and remissions of the disease.

Examination of the blood of 100 persons in New Orleans, selected at random, showed in five instances the bizarre forms of red cells characteristic of this disease.

THE RESULT OF ONE COURSE OF TREATMENT WITH OIL OF CHENOPODIUM ON A GROUP OF PATIENTS HEAVILY INFESTED WITH INTESTINAL PARASITIC WORMS. H. W. BUTLER, M. Clin. N. Amer. **11**:1221, 1928.

A group of 180 children heavily infested with intestinal parasitic worms were treated as follows: Boys between the ages of 8 and 10 years were given 0.6 cc. of oil of chenopodium, and those between the ages of 10 and 12 were given 1 cc. On the evening before treatment, each was given 30 cc. of a saturated solution of epsom salt. At 10 the next morning, each was given 0.3 cc. of the oil. At 2 p. m., a second dose was given, 0.6 cc. to the older and 0.3 cc. to the younger group. At 6 p. m., a second dose of 30 cc. of saturated solution of epsom salt was given. Nearly 17 per cent of the children were entirely cured by the one course of treatment.

Chenopodium is a neurotoxin, and may produce untoward symptoms. These may be prevented by free postvermicidal purgation. Free purgation before administration of the oil is advisable in order to remove mechanically as many parasites as possible. The author believes that the oil of chenopodium is the best general vermifuge.

SMITH, Ogden, Utah.

TWO CASES OF MULTIPLE EXOSTOSES. ERIC A. CROOK, Proc. Roy. Soc. Med. **21**:222 (Dec.) 1927.

A boy, aged 4 years, showed exostoses of the long bones. There was no history or evidence of rickets. The family history revealed that the great-grandfather, grandfather, father and two uncles all suffered from the same condition. The second case was in a boy of 8 years. He exhibited exostoses of the long bones, ribs, clavicle and scapula. His father had exostoses. The patient did not give a history or did not show any evidence of rickets.

GROSS ENLARGEMENT OF THE LIVER. T. M. LING, Proc. Roy. Soc. Med. **21**:228 (Dec.) 1927.

In an infant, aged 3 months, nothing abnormal was found except great enlargement of the liver until one week after admission, when a mass was palpable under the left costal margin. The author suggested as a tentative diagnosis a primary new growth of the kidney with a rapidly growing secondary deposit in the liver. Possibly the mass on the left side was the spleen displaced by pressure of the liver.

WILLIAMSON, New Orleans.

BLOOD EOSINOPHILIA IN ASCARIASIS. K. HILLE, Arch. f. Kinderh. **83**:56 (Jan. 5) 1928.

Eosinophils were found to average about 6 per cent in patients with ascariasis. However, this was an average, as about two fifths of the cases were under 6 per cent, especially those with a lighter infection and only a few worms. In many of the cases the eosinophils would disappear the day after a rise in temperature to return in two or three days to the normal figure.

THE OPEN AIR TREATMENT OF PNEUMONIA IN CHILDREN. P. REYHER, Arch. f. Kinderh. **83**:241 (March 23) 1928.

Except in cases of septic pneumonia, the open air treatment of pneumonia in children is recommended as being superior to other methods. It has a decided narcotic effect, improves the circulation, eases the respiration and ameliorates the cyanosis. The effect on the vegetative nervous system is the outstanding result of the treatment. When this is not able to react, as in the cardiac, atonic, septic and alimentary types, the treatment is without avail.

ACUTE TRANSVERSE MYELITIS AS A FORM OF ACUTE ANTERIOR POLIOMYELITIS. C. HÜNERMANN, Arch. f. Kinderh. **83**:251 (March 23) 1928.

Hünermann adds another form of poliomyelitis to the many atypical variations. A boy, aged 14, had a partial paralysis of the legs and of the sphincters of the bladder and rectum for two days. He had a slight rise in temperature. The spinal fluid did not contain organisms, but as the cell count was increased and as there were 13,000 total white cells in the blood, meningococcus serum was given. Methenamine was given later. Improvement did not occur, and the diagnosis of poliomyelitis was made later. This type of acute poliomyelitis should be called a transverse myelitic form.

THE SEQUELAE OF ENCEPHALITIC PARKINSONISM. J. S. GALANT, Arch. f. Kinderh. **83**:265 (March 23) 1928.

In five patients with parkinsonian encephalitis, from 14 to 32 years of age, all suffered later from some physical and mental disturbances. This was commonest as a rigid and hypertonic musculature and as a lack of fine cerebral discrimination.

MEDIASTINAL PLEURITIS IN CHILDREN. P. REYHER, Arch. f. Kinderh. **83**:276, (March 23) 1928.

Mediastinal pleuritis occurs fairly frequently. A series of twenty-six cases are discussed. It is frequently a complication of mild pneumonia. The diagnosis is made by the x-ray, following atypical symptoms of pneumonia. The x-ray shows a thickening along the mediastinal region somewhat like enlarged peribronchial glands. The treatment is entirely symptomatic. The prognosis is excellent—only one of the twenty-six patients died. This was a tuberculous child, aged 3 months. The course is from eight days to two weeks.

SANFORD, Chicago.

FAMILIAL INCIDENCE OF CONGENITAL MYXEDEMA. N. JOHANNSEN, Acta Paediat. **7**:179 (Nov.) 1927.

Two sisters were cretins, and of three other siblings that had died before they were 1 year old the author strongly suspected on the basis of the history and a hospital report of physical manifestations that one other was similarly affected.

MCINTOSH, Baltimore.

Nervous Diseases

STUDIES IN STUTTERING: III. L. E. TRAVIS and L. B. FAGAN, Arch. Neurol. & Psychiat. **19**:1006 (June) 1928.

In the authors' third article in the study of stuttering, it was found that during stuttering, an increase in amplitude in the knee and achilles reflexes took place comparable to the speaking period of normal speakers. Normal speakers have a greater amplitude during speech than during silent periods. When the stutterer is speaking freely, in contrast to the period of free speech of normal speakers, the amplitude of the two reflexes is less than during silent periods. The variations in resistance offered by the pendant hand to an unexpected blow are directly comparable to these reflex variations.

SANFORD, Chicago.

ENURESIS. JOSEPH K. CALVIN, J. A. M. A. **90**:820 (March 17) 1928.

Various theories regarding anomalies of the bladder and its innervation have been advanced to account for enuresis, but as most patients can be cured without these supposed defects being corrected anatomically they may be considered overrated in their importance. The immediate causes are either organic or physical disturbances, or formation of bad habits due either to lack of proper training or to

an oversensitive nervous system, or both. The chief causes of failure to train the child properly are: postponing the training beyond the natural age; arousing fear concerning the ability to control the bladder, by shaming and punishment; arousing a feeling of antagonism as a result of the spirit of training; emotional scenes on the part of the mother or nurse concerning the use of the toilet, such as showing great concern over accidents; excessive "babying" by overaffection; masturbation, and emphasizing organic ailments to the children, such as speaking of "weak kidneys," or "weakness of the bladder." Most patients can be cured within a few weeks' time, but the utmost cooperation of the parents is essential. Any physical defects should be corrected if possible, and general dietary and hygienic methods instituted. Psychotherapy through proper instruction of the mother is necessary to eliminate the psychologic causes of bedwetting. After fear and anxiety and emotional scenes have been eliminated, confidence that the child can be cured must be restored. Sedatives such as phenobarbital are of value, especially in the nocturnal cases. Belladonna or atrophine are helpful in those who frequently desire to urinate in the daytime. Change of environment is often one of the easiest ways of curing enuresis.

ENCEPHALITIS AS A COMPLICATION OF MEASLES. J. H. MUSSER and GEORGE H. HAUSER, J. A. M. A. **90**:1267 (April 21) 1928.

During an epidemic of measles, 351 cases were seen. In some of the small children, irregular, neurologic symptoms occurred, which seemed to depend on irritation of the meninges with a concomitant increase in the intracranial pressure, or to be the result of pathologic processes in the encephalon. Eight of these cases came to autopsy. The striking gross feature was the presence of numerous discrete punctate hemorrhages throughout the brain. Microscopically, the observation peculiar to this type of encephalitis was perivascular hemorrhage about some of the small vessels of the brain. Postmortem evidence of tuberculosis or syphilis was not found.

BONAR, Salt Lake City.

THE PROBLEMS OF ADOLESCENCE. HERBERT J. CRONIN and ELIZABETH ANN SULLIVAN, New York State J. Med. **28**:69 (Jan. 15) 1928.

Associated with the physical changes of adolescence are many psychic or mental changes which lead to maladjustments. The plastic mind of early childhood is susceptible to injury, and it is only by study of the child's mind that such injury can be avoided.

The subject is discussed under four heads: (1) tantrums; (2) phantasy or day-dreaming; (3) feelings of inferiority; (4) escape from reality.

AIKMAN, Rochester, N. Y.

STUDIES IN THE PSYCHOLOGY OF CHILDHOOD. J. S. GALANT, Arch. f. Kinderh. **83**:170 (Feb. 17) 1928.

This is a continuation of the series already published. Parts 26 and 27, which make up this article, deal with examples of the desire for leadership in the child, and the development of love in childhood through dolls and mother devotion.

ENCEPHALOGRAPHY IN A CHILD WITH PORENCEPHALIA. K. SALOMON, Arch. f. Kinderh. **83**:175 (Feb. 17) 1928.

A child, aged 6 days, delivered spontaneously but after a posterior occipital position, presented stupor, with a preference for a left-sided position, and some dyspnea. The frontal bone was pushed in so far that the anterior fontanel was hardly palpable. The front part of the head was therefore much smaller in proportion than the back. Four days later, following a continuation of the symptoms, an encephalogram was taken, showing porencephalia. The child died a week later, and autopsy showed an immense porencephalic defect.

SANFORD, Chicago

PSYCHOLOGIC PROBLEMS OF HUNGER AND APPETITE PARTICULARLY IN THE YOUNG CHILD. D. KATZ, Ztschr. f. Kinderforschung **34**:158, 1928.

Katz discusses the general problem in an interesting manner and then recounts his experiences with his own children, aged 6 and 8 years, respectively. He found a relation between the constitution of the children and their appetites and tastes. Thirst seems to be a much more immediate and primitive sensation, for whereas a child will spontaneously call "for liquids," an interesting activity will so absorb it that there will not be a request for food unless through the sight or smell it is reminded of its obvious hunger. Katz also found that hunger was dependent on such conditions as time and place. Hunger was suppressed entirely by an irregularity in otherwise regular habits. Dislikes for particular foods can be a matter of imitation of adults or older brothers. Katz did not attempt to force such food unless it was clearly a question of caprice.

REICHLE, Cleveland.

PREMATURITY AS A FACTOR IN NERVOUS AND MENTAL DISORDERS OF CHILDREN. CARL LOOFT, Acta Paediat. **7**:15 (Nov.) 1927.

In a review of Little's original articles and of continental literature since that time, the author finds that the majority of writers, with the notable exception of Little and Ylppö, give a good prognosis for mental development following premature birth and conversely tend to ascribe to syphilis the responsibility for a large proportion of the cases of feeblemindedness and spastic paralysis encountered in pediatric practice. The author considers that both of these tendencies are at variance with the facts. From a study of 129 premature infants, weighing less than 2,500 Gm. at birth, he found that 24 per cent showed subnormal mental development varying from mild inferiority to idiocy; one patient developed Little's disease. Among 532 backward children in the public schools of Bergen, the mental status of 29 or 5.5 per cent, could not in his opinion be attributed to any other factor than prematurity; of these, 4 showed motor symptoms, including 2 with Little's disease. The author then examined the birth histories of all the pupils in the first grade of the primary schools in one year and found 15 who had weighed less than 2,500 Gm. at birth; of these, one showed mental inferiority by the Binet-Simon test. In another group of 105 premature infants seen in the author's practice during the past ten years, there were 19 with mental inferiority, among whom 9 showed motor nerve symptoms. Finally, examining the records of imbeciles from special schools in all parts of Norway, the author selected 326 histories which were considered to give reliable information about the condition at birth, and in these found 32, or 10 per cent, who had been born prematurely. Syphilis was felt to be excluded as a factor in the first group quoted and also in the group from the author's own practice, and the rôle which syphilis plays in causing feeblemindedness and Little's disease is considered to be a subordinate one, merely in its tendency to predispose to premature birth. Hereditary inferiority and alcoholism are also thought to play a minor part. The author concludes that prematurity, by reason of its association with cerebral hemorrhage at birth, is an important cause of mental and nervous disorders of childhood.

MCINTOSH, Baltimore.

Diseases of the Ear, Nose and Throat

OTORRHOEA AND THE FAMILY DOCTOR. GEORGE B. MCAULIFFE, M. J. & Rec. **127**:117 (Feb. 1) 1928.

The author believes that the general practitioner should be able to take care of patients with diseases of the ear. He should equip himself with an electrical otoscope and syringe (the procedure of syringing is described in the paper) and so be in a position to make an aural examination. He can have a roentgenogram made of the mastoid, and he can have a culture made from the discharge; he

can also have a laboratory determination made of the calcium content of the pus to ascertain whether the bone is breaking down.

A description of how to examine for the various diseases of the ear and the different methods of treatment are given in detail.

WILLIAMSON, New Orleans.

NASOPHARYNGEAL INFECTIONS AS A CAUSE OF DYSPEPSIA, CHOLERA INFANTUM AND SEPTICEMIA IN INFANTS. H. ERNBERG, Acta Paediat. **7**:87 (Nov.) 1927.

The author finds that more than two thirds of the patients admitted to his hospital with the diagnosis of acute dyspepsia, cholera infantum and septicemia showed signs of nasopharyngitis on admission, and concludes that infections of the upper respiratory tract form the starting point of the majority of digestive disturbances of infants and young children.

MCINTOSH, Baltimore.

Surgery and Orthopedics

CONGENITAL PYLORIC STENOSIS IN ADULT LIFE. BURRELL B. CROHN, J. A. M. A. **90**:197 (June 21) 1928.

The author reports the case of an adult in which there was a history of forceful uncontrollable vomiting from shortly after birth up to the time of operation, when the pylorus was found markedly stenosed, but softer than usually felt in congenital hypertrophic pyloric stenosis. This case suggests the possibility that patients treated medically and relieved of symptoms might carry the condition over into adult life.

BONAR, Salt Lake City.

CHRONIC APPENDICITIS IN CHILDREN. A. J. WALTON, Lancet **214**:595, 1928.

Of 601 cases of acute appendicitis, 186 patients were under 14 years of age; 106 were males and 80 females. In the chronic group of 305 cases, there were only 33 cases in children under 14 years of age; 17 were females and 16 males. Further analysis of these 33 cases of chronic appendicitis showed that:

1. *Following Acute Attacks.*—In seventeen cases the operation followed a few weeks or at most a month or two after a definite acute attack. In all the attacks had been typical. These cases, therefore, should more correctly have been included with the acute group and not among the chronic. "They are, however, a very important group from a practical point of view, for if the assumption is correct that appendicitis in adults or in children practically always commences with an acute attack, it becomes of very great importance to recognize that such attacks are alarmingly frequent in young children, and that acute appendicitis still has a very high mortality among them in spite of the efforts of modern surgery."

2. *Cases with Enlarged Mesenteric Glands.*—There were five cases in which the only lesion found was a subacute or chronic inflammatory change in the mesenteric glands, especially the glands of the ileocolic angle. The symptoms may closely resemble those of appendicitis. The majority of the investigators appear to hold the view that the glands are tuberculous and that the source of the infection is in the lower ileum. The author has found these glands enlarged in many cases of acute appendicitis. In all such cases the appendix should be removed, even if it is not the source of the infection. However, it is to be remembered that the symptoms may not be cured and may recur as before after a short interval of freedom.

3. *Cases of Visceroptosis.*—Five cases occurred in young girls of 13 who had suffered from frequent attacks of pain in the right iliac fossa and the lower part of the abdomen. All were characterized by the fact that there had been a large number of attacks lasting only for a few days, associated with vomiting and

pain, and in some cases even with pyrexia, but the condition did not progress. After removal of the appendix and division of the membranes and bands, the symptoms were for a time relieved, but they returned again later. There was never any evidence of local formation of tumors in these cases.

4. *Threadworms.*—There were four cases in which there had been mild attacks suggestive of appendicitis and in which at operation the appendix appeared to be slightly inflamed. In every case it was removed and on section many threadworms were found in its lumen.

5. *Lack of Pathologic Lesions.*—In two cases pathologic lesions of any sort were not found, but the patients remained well after operation.

"My own cases failed to reveal a single case of appendicitis chronic from the beginning, unless we consider as such those where threadworms were present in the lumen, and I am, therefore, left with the opinion that such a condition does not exist. In children, unlike adults, the majority of patients diagnosed as chronic appendicitis are in reality suffering with acute lesions of this or some other viscus and ought to be operated upon without delay."

LANGMANN, New York.

Miscellaneous

SUPERVISION OF THE HEALTH OF THE PRESCHOOL CHILD. ITS RELATION TO THE EARNING CAPACITY OF THE WAGE EARNER. HUGH CHAPLIN, New York State J. Med. **28**:20 (Jan. 1) 1928.

Industrial medicine, at first limited to treatment and later to the general medical supervision of the worker, should be extended to include the care of the children of the worker.

AIKMAN, Rochester, N. Y.

CARRIAGE AND LENGTH OF THE BODY IN THE FIRST YEAR OF LIFE. M. HOHLFELD, Arch. f. Kinderh. **83**:1 (Jan. 5) 1928.

In a study of thirteen children under 1 year of age, a decrease in sitting height of from 0.65 to 1.6 cm. was found by allowing the children to sit up for quarter hour periods, up to one hour. When they stood for one hour periods, the decrease in standing heighth was from 0.85 to 1.7 cm. Believing that this might be due to a flattening of the arch of the foot, the author added weights for the children to support. This further decreased the standing height.

OBSERVATIONS ON THE TEMPERATURE OF CHILDREN AT A HEALTH RESORT. A. MERTZ and A. CHASSEL, Arch. f. Kinderh. **83**:18 (Jan. 5) 1928.

The variations in the temperature of fifty children between the ages of 4 and 15 years were studied intensively. The children were at a health resort mostly for treatment for tuberculosis. It was found that the axillary temperature was the most satisfactory. The authors consider the temperature curve to be the greatest diagnostic aid as an indication of the results of treatment in tuberculous children.

SANFORD, Chicago.

Society Transactions

AMERICAN PEDIATRIC SOCIETY

HOWARD CHILDS CARPENTER, M.D., Secretary

Fortieth Annual Meeting, April 30-May 1-2, 1928
First and Second Sessions

HENRY L. K. SHAW, M.D., *President, in the Chair*

Opening Session, 9:30 A. M., April 30, 1928

PRESIDENTIAL ADDRESS. Pediatrics One Hundred Years Ago. Presented by John Claxton Gittings.

This paper has been published in full in a previous issue (*Am. J. Dis. Child.* **36**:1 [July] 1928).

FREQUENCY OF LOBAR TUBERCULOSIS OF THE LUNG IN INFANCY. DR. P. F. ARMAND-DELILLE. (Read by Title.)

THE USE OF DEXTROSE INTRAPERITONEALLY IN INFANTS AND YOUNG CHILDREN. CLIFFORD G. GRULEE and HEYWORTH N. SANFORD (by invitation).

Five per cent dextrose solution given intraperitoneally may prove a valuable therapeutic measure in a variety of conditions in children provided the dextrose is sterilized in the dry state, and the solution made up immediately before using. The dextrose is prepared by autoclaving 5 cc. of chemically pure dextrose in a dry, sterile tube at 15 pounds for twenty minutes. The tube is especially prepared by plugging the top with a cartridge containing calcium chloride. One hundred cubic centimeters of sterile water is added to the dextrose just before using.

This solution has been given in 76 cases, totaling 432 injections. The diseases for which it was given include: severe dehydrating diarrhea, decomposition, lobar and bronchopneumonia, pyelitis, tonsillitis and postoperative conditions. To be effective, the solution of dextrose must be frequently given intraperitoneally. In one case, six injections a day were given for several days.

Seven deaths occurred in the series. One patient who died from intoxication had entered the hospital in a moribund condition. Of fourteen patients with bronchopneumonia, four died; in one of these the condition was complicated by a congenital heart defect. Another death followed an operation for intussusception, and the last was in a patient with florid syphilis. In only the last case could death be in any way attributed to the use of dextrose. In this case the child developed shock after two injections of neoarsphenamine and dextrose.

Besides the fatal case of syphilis, one patient with intoxication showed abdominal distention after the injection of dextrose. Both of these cases occurred during the same period, in which the usual brand of dextrose was not used and in which the calcium chloride was granular instead of porous. It is thought that either or both of these changes may have been a factor in the result.

DISCUSSION

DR. D. MURRAY COWIE, Ann Arbor, Mich: We have used dextrose intravenously in our clinic for many years, to a lesser extent intraperitoneally. We at

first overcame the reactions following the injections of dextrose by autoclave fractional sterilization. We came to the conclusion that the reaction was due to caramelization of the solution. Solutions with the slightest color gave reactions, while clear solutions did not.

Our experience in the subcutaneous use of bacteriophage filtrate obtained from sewage water led us to have confidence in the safety of filter sterilization. We adopted this method in the preparation of our solutions of dextrose for intravenous and intraperitoneal injection. We have been using these filtered solutions for the past three years. Rarely do any reactions occur. With sterile filters and sterile glassware, this means of preparing solutions of dextrose is simple and comparatively rapid.

DR. KENNETH D. BLACKFAN, Boston: The use of injections and solutions intraperitoneally, as first used by Maxy and myself, was referred to. This method was suggested by the late Dr. Howland on his return from London in 1915, where for some time they had been using intraperitoneal injections in the Great Ormond Street Hospital. I think there is a reference made to it in the book which is now published by Garrod, Batten and Thursfield.

DR. CHARLES G. KERLEY, New York: My results with the use of dextrose intraperitoneally have not been satisfactory, nor has the intraperitoneal use of any other solution seemed to warrant the risk taken. By hypodermoclysis and transfusion, one can accomplish all that is supplied by the peritoneal route without danger.

DR. FRANK C. NEFF, Kansas City, Mo.: The use of concentrations of dextrose stronger than 5 per cent, as Dr. Grulee said, may be definitely dangerous. I am not sure that even 5 per cent would be tolerated in all instances. In two children suffering from ileocolitis in whom 5 per cent dextrose had been injected intraperitoneally, it was found, a few hours after injection, that at a second puncture of the peritoneum considerably more fluid was present than had been put in. Peritonitis was not present. So, I think it is a good point to use this method of treatment only with weak solutions and not at all in a child who has a feeble circulation.

DR. OSCAR M. SCHLOSS, New York: I have had experience with dextrose solutions for about fifteen years. I have used a hypertonic solution of dextrose for intravenous injections. A 10 to 15 per cent solution is used with the idea of temporarily increasing the osmotic pressure of the blood and also on account of the food value of the dextrose.

Dextrose solutions turn acid after autoclaving, and the acidity increases rapidly. Any ill effect can be prevented by preparing the solutions fresh each day or by buffering. I rely largely on the former and rarely have reactions from intravenous injections of freshly prepared solutions. Old solutions can cause severe reactions and even death.

The method of preparation devised by Dr. Grulee should prove useful.

I have had little experience with the intraperitoneal injection of dextrose solutions owing to their irritating effect. It has been shown by Denzer and Anderson, Cunningham and others that solutions injected into the peritoneal cavity practically always cause an inflammatory exudate. Dr. Grulee used smaller amounts than are usually employed, which may cause less irritation than larger amounts.

DR. HENRY F. HELMHOLZ, Rochester, Minn.: Another thing that must be considered in the administration of sugar solution is that with injections of such solutions there is a tendency on the part of the body to bring the solution injected

up to a salt content that corresponds to about two thirds of the amount of salt in the blood; hence, it would seem that when sugar solution was given it might be advantageous to use Ringer's solution rather than a watery solution to avoid this difficulty.

DR. SAMUEL AMBERG, Rochester, Minn.: Dr. Grulee has taken into consideration the subcutaneous and intravenous route of injection. In a few cases I have used the intramuscular route with freshly prepared solution in 100 cc. amounts, with satisfactory results.

DR. GRULEE (closing): Regarding Dr. Blackfan's question as to the Eli Lilly preparation, I have not used it, but Dr. Sanford has used it on dogs and says that it works well.

In answer to Dr. Kerley's question regarding the advantages of giving the solution intraperitoneally over subcutaneously or intravenously, I do not believe that I would have the temerity to use subcutaneously or intravenously the quantities that are sometimes required.

For instance, in a small infant weighing 7 or 8 pounds (3,175.14 or 3,628.74 Gm.) I would hesitate to try to inject 100 cc. of 5 per cent dextrose intramuscularly or subcutaneously or intravenously five or six times a day. Yet we found it necessary to give that amount and were apparently justified.

As to the question that Dr. Helmholz has raised about the addition of Ringer's solution, I would say that perhaps that was justifiable, but I think Hartmann has recently brought out in a paper the fact that sodium chloride solution injected intraperitoneally in all persons with intestinal intoxication rather increases than reduces the acidosis. And we have not been using the dextrose with any physiologic sodium chloride or Ringer's solution, not because of that but because we did not have untoward results. I do not feel that this is accomplished without any reaction in the peritoneum, of course. Recently, for example, in giving blood intraperitoneally to a patient with a bad form of anemia, complicated by a large spleen, we had reason to advise removal of the spleen, which was done.

At the time of operation definite adhesions were found, so that one cannot regard intraperitoneal injections as without any hazard. It seems to me, however, that there is a definite need for them in persons with intestinal intoxication. So far as I have seen, it has given the best results in those cases.

ABDOMINAL PAIN IN CHILDREN DUE TO ENTEROSPASM. HENRY HEIMAN and PHILIP COHEN.

There is a type of pain common and peculiar to children from the ages of 4 to 12 years. The pain is usually referred to the umbilical region, and less often to the right and left iliac fossae and to the epigastrium. The characteristic feature of this pain is its frequent recurrence. Ingestion of food usually brings on the colic, but this may not bear any relation to meals, and often the mere sight of food causes an attack. The pain may be only slightly disturbing or so severe as to simulate a renal or gallstone colic. Vomiting, anorexia, constipation or an urgency of defecation are the usual concomitant symptoms.

The children afflicted with this condition often exhibit such incidental symptoms as vasomotor instability, enuresis and laryngospasm; they complain a good deal of pains in different parts of the body and have excessive perspiration or salivation. This picture strongly suggests the vagotonia described by Eppinger and Hess. Most of the other children suffering from this abdominal pain present a pronounced neuropathic make-up. Emotional factors are usually at the basis of the attacks of colic. Distaste for food, haste to get away from the table, excite-

ment, play and maladjustment with environment are examples of this. Infection, which is now well known to affect intestinal movements and the intestinal gradient, is a second important etiologic agent.

The physical examination gives negative results except for the chance finding of a spastic intestine, which feels cordlike and soft to the finger and rolls easily under the touch. The negative examination and history of recurrent attacks exclude the diagnosis of appendicitis. Pyelitis, renal calculus, lead colic, worms, Henoch's purpura and urticaria of the intestine are to be eliminated as possibilities.

Atropine given in physiologic doses affords a ready and prompt relief. It is best given one half hour before meals. This is a relief and not a cure, which rests on the treatment of the fundamental vagotonia, for which calcium therapy has been suggested, or the neuropathic constitution, for which suggestion and other psychic treatment have been advocated by Czerny and Kleinschmidt. We have had excellent results, simply by administering atropine intermittently, according to the frequency of the attacks.

Roentgen-ray studies are difficult, for it is impossible to time the spasm of the intestine for the hour of the roentgen-ray examination. We were fortunate, however, in obtaining in a few cases roentgenograms of pylorospasm, spasm of the colon and hypertonicity and hyperperistalsis.

We prefer the term of enterospasm to the one of "Nabelkolik" applied by Moro and adopted by subsequent German writers. The clinical and roentgen-ray evidences point to a spasm of the intestine, usually the ileocecal region or the colon, as the cause of the abdominal pain, and hence the term of enterospasm gives a better insight into the pathologic function of this common condition of children.

DISCUSSION

DR. CHARLES HERRMAN, New York: As Dr. Heiman indicated, this is probably one manifestation of a functional neurosis in the gastro-intestinal tract. I think the best explanation is to be found in an article appearing about two years ago in the *British Medical Journal* by Frazer, in which he points out, I think, conclusively that one is dealing here with a distinct functional neurosis, a neuromuscular disturbance. He goes into the subject more from the evolutionary standpoint and shows that the sympathetic system phylogenetically is older than the parasympathetic system, and that in the lower animals an adjuster is not present, simply a receptor and effector without an intermediate adjustor.

In these children, one finds contractility without the inhibitory function, and it is practically the same in intussusception and pyloric spasm.

In discussing the question of pyloric stenosis and the benefit from atropine, Dr. Haas pointed out that pyloric stenosis was only one form of a neuromuscular disturbance, which might also manifest itself in other parts of the body.

DR. D. MURRAY COWIE: I should like to cite a case of phantom tumor that occurred in our clinic last year to illustrate the large amount of atropine that a child with enterospasm can take. The tumor was in the upper right quadrant of the abdomen, and was probably 5 inches long by 2 inches in diameter. It would come and go, sometimes remaining for long periods. The child was emaciated, was in almost constant pain and vomited almost all food given to him. I thought that the tumor was due to two segmenting contractions of the circular muscle of the colon in spasm.

The slide illustrates the progressively increasing doses of atropine, the weight curve, and the pain curve, as constructed on the number of marked spasms the child had during the day. Treatment was started with 1/300 grain (0.18 mg.) of

atropine sulphate, increased in the following order: 1/200, 1/150, 1/100, 1/50, 1/30, 1/20 (0.12, 0.4, 0.6, 1.3, 2.3) three times a day; the dosage was continued at 1/20 for seventeen days, then gradually reduced to 1/50 in the course of ten days and then to 1/60 (1 mg.) twice daily ten days later when he was discharged.

The pain did not materially improve until 1/30 grain was reached. The weight curve began to increase at this point. After three weeks at home, the patient returned without any symptoms. He was advised to discontinue the atropine and report in a week. He did not report, however, until three months later when he returned for tonsillectomy, still not showing symptoms without the use of atropine. During this period his weight had increased from 39¾ to 49 pounds (18 to 22.2 Kg.).

It seemed remarkable that a child could take so much atropine without any untoward symptoms. The child did not have a rash, excessive thirst or dryness of the mouth. The atropine has to be continued over a long period just as in the case of the hypertonic infant.

In answer to the question of whether the ciliary muscles were affected in this case, at one time the pupils became much dilated but always reacted to light. There were no visual symptoms.

Dr. Heiman (closing): I have nothing to add, except that I am grateful to Dr. Herrman for giving the explanation in regard to the etiology of the nervous symptoms.

Encephalitis in Children, with Special Reference to Toxic Form. Dr. Thomas B. Cooley. (Read by title.)

The Control of Infection in Rheumatic Children. Hugh McCulloch and Edith I. M. Irvine-Jones (by invitation).

A study of 150 children observed in the heart clinic of the St. Louis Children's Hospital was undertaken to find out how far infection of the upper respiratory tract played an etiologic rôle in rheumatism and chorea and how far the control of such infection influenced this disease as judged by the number of recurrences. The well known seasonal variation in the occurrence of the disease was confirmed. The majority of the attacks occurred in the spring and to a lesser extent in the winter. This is comparable with the seasonal incidence of infections of the upper respiratory tract in St. Louis. The relation of such infections to the occurrence of rheumatic fever was studied in two ways: (1) by considering those cases in which the infection precipitated the attack, and (2) by considering the incidence of such infections between attacks of rheumatic fever. It was found that out of 304 attacks, 98 were preceded by frank tonsillitis, 74 were preceded by a "common cold" and in 25 the history was "cold with sore throat." Zymotic diseases and pyogenic infections preceded 36 of the attacks. In 28 instances a history of infection could not be elicited and in the remainder of the cases it was not known. The figures for the occurrence of colds and sore throats without accompanying fever in rheumatic subjects shows the increased incidence of such infections. Ninety-five subjects suffered from frequent infections of the upper respiratory tract, 15 had few such infections and 38 did not have colds and sore throats in the absence of rheumatic fever. (In 18 persons of this group the attack of rheumatic fever was always preceded by a cold or sore throat.)

A study of the rôle played by tonsillectomy in the prevention of further attacks of rheumatic fever was made by dividing the subjects into three groups: (1) those who were tonsillectomized before their first attack of rheumatic fever;

here the average number of attacks was two per person; (2) those not tonsillectomized, the average number of attacks per person being 1.76; (3) the subjects tonsillectomized during observation. Here the average number of attacks before operation was 1.53; after operation, 0.64. Tonsillectomy as a preventive in further attacks of rheumatic fever has been discredited in recent years by Kaiser and others, and we feel that our more encouraging results are due to the aftercare of the upper respiratory tract in such cases.

A study of the benefit to be derived from prolonged care in a convalescent home was also made. It was found that on a basis of 100 children who spent a certain time at Ridge Farm (a convalescent home) the number of acute attacks at the farm would be 7, while the same group at home for a similar length of time would have 37 attacks. This striking difference was thought to be due to the rarity of infections of the upper respiratory tract at Ridge Farm. This freedom from attacks during the stay at the farm was only temporary, however, as it was found that such children, subsequent to care at Ridge Farm had an average of 0.74 recurrences against 0.46 in a comparable group treated at home for a similar length of time.

The most encouraging figures in the care of rheumatic children were obtained from a study of subjects who had intensive care directed toward the eradication of nasopharyngeal infections. In eighty of the subjects who have been watched for more than a year, it was found that infection was constantly present in the nose and throat. These subjects could be divided into two groups, those who cooperated in the measures recommended and those who did not. Of the group in which cooperation was good and the nasopharyngeal infection improved or eradicated, 10 per cent had recurrences. When efforts were less successful in treating the infection, recurrences occurred in 16.6 per cent. As a comparison, the uncooperative group showed recurrences in 50 per cent of the subjects, and in all but two cases the nasopharynx remained infected.

An outline of therapy used in rheumatic children includes the institution of general hygienic measures in the home, sunlight, ventilation and avoidance of overcrowding with its attendant cross infections. The children and parents are instructed as to suitable food, adequate rest and outdoor activity. The children attend the clinic regularly in the winter but at long intervals during the summer. Local measures insisted on include dental care and tonsillectomy in most cases. The nose and throat are kept clean by the use of antiseptic instillations for the former and gargles for the latter. Acute infections of the upper respiratory tract are regarded as serious and so treated. The treatment of chronic infection in the nose and throat is not altogether satisfactory, but it is thought that the general hygienic measures instituted and local treatment such as irrigation are of assistance.

STREPTOCOCCUS HEMOLYTICUS IN THE NASOPHARYNX OF CHILDREN. DR. H. F. HELMHOLZ and MARION R. BOWERS.

The infections of the upper respiratory tract which occur periodically in somewhat epidemic form are of various types. Some are associated with otitis media, some are characterized by cervical adenitis, others by abdominal symptoms, or the predominant symptom may be infection of the eyes or a diffuse redness of the membrane of the nose and throat.

The etiology of the common cold is generally considered unknown. Various types of streptococci, staphylococci, *Micrococcus catarrhalis, Bacillus influenzae* and even a filtrable virus have been considered etiologic organisms. The work of Kraus and Foster has not been substantiated by recent investigation and that

of Dochez and his associates has shown that various filtrable gram-negative bacilli are less numerous in cultures from throats of persons with acute colds than in normal persons.

It is generally agreed that the organisms most frequently found in the nasopharynx are *Micrococcus catarrhalis* and *Streptococcus viridans*, the latter being present in from 90 to 100 per cent of cases. Reports in the literature show the greatest variation in the percentage incidence of *Streptococcus hemolyticus*. Blomfield, taking cultures weekly from six healthy persons for three months, did not once find *Streptococcus hemolyticus*. On the other hand, Dochez and his associates found it in 17 per cent of their cultures. Davis found it in 60 per cent of 105 swabs taken from forty-five medical students.

Our study is based on cultures of nasopharyngeal swabs taken biweekly in a series of seventeen children, from 2 to 14 years of age. Swabs were taken in the homes of the children, great care being exercised to bend the wire applicator so as to avoid contact with any portion of the mouth and to touch only the nasopharynx. The swabs were then taken to the laboratory, rinsed in 2 cc. of physiologic sodium chloride solution and 2 drops put in a petri dish and plated in 5 per cent blood agar.

In the summer months *Streptococcus hemolyticus* was found infrequently in swabs from the control patients and from those with infections. Positive cultures began to increase in number in the middle of September. During the other months, with the exception of December and November, 15 to 34 per cent of the cultures in the control patients were positive. In every month except September, the incidence of *Streptococcus hemolyticus* was greater in the cultures from children with respiratory infections, ranging from 26 to 62 per cent. In a group of school children from whose throats cultures were made during a mild epidemic of scarlet fever, there was a higher incidence of streptococci in those with acute infections.

In the control group *Streptococcus hemolyticus* was associated with sixteen infections of the upper respiratory tract, but in twenty-two instances of infection it was not found. In fifty-six instances it was found when there was no evident infection. Of the children of the control group whose cultures showed more than 10 per cent of streptococci, 35 per cent had respiratory infections, and of those whose cultures showed less than 10 per cent of streptococci, only 12 per cent had evident nasopharyngeal disease.

The incidence of streptococci in the family groups varied. The average number of positive cultures for each person for the entire period ranged from 1.5 to 9. There were three families with two children; in one, cultures were positive three out of four possible times on the same day in both children; in the second, seven out of ten were positive, and in the third, one of two were positive. In another family of four children each child had a positive culture on the same day once, and in four instances three of the children had positive cultures at the same time. In a family of five children, there were only two instances in which two were positive at the same time.

The incidence of streptococci in the cultures was greater during the periods from September 9 to September 15, and from November 26 to November 30, when eight of the seventeen control patients gave positive cultures. From November 8 to November 15 seven were positive, and on four occasions six were positive. On August 8 and from August 25 to 30, not a single culture was positive for *Streptococcus hemolyticus*. From July to March, hemolytic streptococci were found in 26 per cent of nasopharyngeal cultures. In 159 patients with infection of the upper respiratory tract 49 per cent of the cultures were positive for *Streptococcus hemolyticus*.

DISCUSSION

DR. MCCULLOCH: This study by Dr. Helmholz is interesting in connection with the work we have been doing on the children with cardiac disease admitted to the Children's Hospital in St. Louis. We have been making cultures from tonsils removed at operation and from washings from the sinuses of these children, and from the material in the nose and throat during and between attacks of rheumatic fever. Our results conform closely to his.

One important observation is the frequency with which *Streptococcus viridans* is present in the nose and throat of these children. It is also interesting to note that there is no predominating type of organism in these children with rheumatic fever. Staphylococci and various forms of streptococci are found. Many have had blood cultures made during the time of attack of rheumatic fever with negative results, even those that show almost pure culture of *Streptococcus viridans* present in the nose and throat.

DR. GITTINGS: There is one part of Dr. McCulloch's paper which I may have misunderstood. That was the statement he made about a certain group of children who had had their tonsils removed early in life and yet who showed severe manifestations of infection.

DR. MCCULLOCH: It is true in general, as I explained briefly, that these children had a higher incidence of attack of rheumatic fever than in a group who had their first attack before tonsillectomy. But these infants had a severe infection which made the tonsillectomy necessary at an early period of life, and for that reason results were probably not so good. We have felt, too, that this was in part due to the fact that tonsillectomy was performed without adequate postoperative care of the nose and throat. This small group further emphasizes our impression that postoperative care following tonsillectomy is imperative to diminish attacks of rheumatic fever.

This is also interesting, in view of the idea prevalent to a certain extent that rheumatic fever and heart disease might be prevented by universal tonsillectomy.

DR. HEIMAN: I have found that whether the children's tonsils were removed or not the rheumatic infections occurred just as promptly and just the same. One must not lose sight of the fact that the oral cavity consists of more than the mere tonsils. The condition may be due to the condition of the intranasal parts or the lymphoid tissue of the tongue and throat. I do not oppose tonsillectomy. I do not wish to be misunderstood. If there is indication for it, I am among the first to suggest the removal of the tonsils if they are hypertrophied, obstructed, shaggy or mushy. And if a child has frequent attacks of tonsillitis I presume also that if any *Streptococcus viridans* or *Streptococcus hemolyticus* are present in that particular organ it requires removal. But I do not want to make the statement that every child should be tonsillectomized. In fact, in my office I oppose the operation in the children who have good tonsils.

DR. H. B. WILCOX, New York: I should like to ask Dr. Helmholz whether the treatment of persons with these infections of the upper respiratory tract occupies a majority of the attention of practitioners in almost every part of the country. More time is lost from such conditions than from all other diseases put together. Nothing is more difficult than to cure, or materially affect, the course of these so-called common colds. As a result of this, it is probable that a good deal of damage is done by the unwise use of a great variety of so-called disinfectants. The nasal mucosa in children is extremely intolerant of local application.

I should like to know, therefore, whether the studies of Dr. Helmholz have resulted in any definite information as to the value of the use of this great variety of nasal drops, douches and sprays?

DR. CHARLES G. KERLEY, New York: It is impossible to say that a given tonsil is not infected. There are probably few tonsils that are not more or less diseased, particularly in children after the second year.

All the patients who have potential cardiac disease, who include in addition to those who have frank rheumatic fever and chorea those who suffer from indefinite pains of the muscles and joints, should have the teeth examined by a competent roentgenologist, the sinuses given proper attention and the tonsils removed, regardless of their appearance. I have found that many of the tonsils which appear the most innocent from their surface aspect are extensively diseased.

DR. CHARLES HENDEE SMITH: As the cause of rheumatism is not known, any hypothesis is acceptable in discussion. In our cardiac clinic we have been removing the tonsils of all children with heart disease, chorea or rheumatism for twelve years. The incidence of recurrence of rheumatic infection is distinctly lower after tonsillectomy than when the tonsils have not been removed. Here is one portal of entry that can be removed. Many of these tonsils are diseased, as Dr. Karley says, when they apparently look fairly healthy. But even tonsillectomy does not stop the recurrence of rheumatism. There remains the large amount of other lymphoid tissue, which cannot be removed.

Similarity between tuberculosis and heart disease has been noted in many respects. I wonder if an analogy cannot be drawn, possibly an inaccurate one, between tuberculosis and rheumatism. It is known that tubercule bacilli remain quiescent in the lymph nodes over a large number of years, only to discharge into the lymph channels through some unknown cause and set up active infection in other parts of the body. There are many chronically enlarged lymph nodes which do not disappear after the tonsils are removed. Is it not possible the lymph nodes are the reservoir for streptococcic infection just as much as for tuberculosis? When the cause of rheumatism is known, then this possibility can be disproved.

DR. KENNETH D. BLACKFAN, Boston: Dr. Zenzer, in making cultures from children who have died from rheumatic fever and endocarditis, has found that the abdominal lymph glands and the spleen may also harbor the streptococcus.

DR. HENRY J. GERSTENBERGER, Cleveland: Some dependable idea can be obtained in coming to a decision as to whether a tonsil should be removed or not from a meticulous and a prolonged study of the condition of the regional lymph nodes. This, at least, has been my experience.

DR. D. MURRAY COWIE: There are cases on record, and I have known of cases of arthritis and rheumatism on a tuberculous basis; tuberculous arthritis, so-called, without any structural tuberculous changes in the joints—in other words, arthritis, periarthritis or rheumatism due to a tuberculous focus at some distant part.

DR. HELMHOLZ (closing): In answer to Dr. Wilcox, I might say that Dr. Stark has been doing some work on experimental irritation of the nasal mucous membrane of rabbits, and has been able to show that water or any sort of watery solution tends to make inflammation in the nasal mucous membrane worse rather than better.

With regard to tonsillectomy, I might say that our nose and throat department puts it squarely up to us. They say, "We cannot tell when the tonsil is infected. If you find in the general examination a good reason why the tonsils should come out, we shall be glad to remove them."

Our five indications for tonsillectomy are: (1) size sufficient to obstruct respiration; (2) recurring acute infection of the tonsils; (3) infection of the ears; (4) acute and chronic swelling of the lymph glands, and (5) the possibility of the tonsil acting as a focus of infection.

With regard to the bacterial content of the tonsil, Davis has shown that in excised tonsils *Streptococcus hemolyticus, Streptococcus viridans,* influenza bacilli and a great many other organisms are constantly present. So it is not the presence of those organisms that apparently is harmful, but when the question of a possible focus of disease arises, the tonsils must always be considered.

Second Session, 8 P. M., April 30, 1928

THE IMPORTANCE OF INDICANURIA, STOOL FAT AND SCHMIDT FERMENTATION TEST IN THE PRACTICE OF PEDIATRICS. ROLAND G. FREEMAN, EDGAR G. MILLER and ROWLAND G. FREEMAN, JR. (by invitation). (Read by title.)

STUDIES IN IMMUNITY: I. NONSPECIFIC FACTORS INFLUENCING THE TUBERCULIN SKIN REACTION. DR. A. GRAEME MITCHELL, DR. WILLIAM B. WHERRY, DR. BERNICE E. EDDY and DR. FRANK E. STEVENSON.

A review of the literature dealing with the effect of nonspecific factors on the tuberculin skin reaction shows that comparatively little work has been done. While many statements are made, they are frequently not substantiated by sufficient evidence. It is, however, stated that the tuberculin reaction may become negative in the acute stage of measles, German measles, chickenpox and influenza and may become positive again during convalescence. There is a difference of opinion concerning the effect of pertussis. Local factors such as anemia, water content of the skin and light are said to influence the intensity of the reaction. It is stated that the injection of foreign protein causes an increased skin response.

Our own studies are summarized in the accompanying table.

Tuberculin Test

		Febrile Stage		Convalescent Stage	
Disease	Number of Cases	Number Positive	Per Cent Positive	Number Positive	Per Cent Positive
Measles	200	7	3.5	30	15.0
Diphtheria	58	8	13.7	12	20.6
Poliomyelitis	32	1	3.1	3	9.3
Scarlet fever	31	3	9.6	7	22.5
Varicella	15	3	20.0	5	33.3
Miscellaneous	15	1	6.6	3	20.0
Total	351	23	6.4	60	17.0

In these studies the same type and amount of tuberculin were always employed in the same patient during the febrile and during the convalescent stage.

It also developed in the course of the study that the degree of local reaction during the acute stage was often less than the same amount of tuberculin would cause during convalescence; that a positive reaction could sometimes be secured during the acute stage by employing a larger dose of tuberculin than was necessary later; that in some cases the appearance of the skin reaction was delayed for three or four days or longer during febrile stages of the disease. Tables were

given which showed that the Dick and Schick tests were more frequently positive during the convalescent stage of certain diseases than during the febrile stage.

It was concluded that a positive skin reaction to tuberculin is approximately from two to four times as frequent during the convalescent afebrile stage as during the acute stage of such diseases as measles, diphtheria, scarlet fever, varicella, poliomyelitis, pneumonia, influenza and gastro-enteritis. There is some evidence that larger doses of tuberculin may cause a positive reaction during the febrile stage of these diseases. Readings of tuberculin reactions during acute diseases should be continued for several days as the skin response may be delayed longer than forty-eight hours.

DISCUSSION

DR. CHARLES HERRMAN: With regard to the tuberculin test in whooping cough a large number of patients with whooping cough are seen at the Riverside Hospital, and a definite relation between whooping cough and tuberculosis has not been found, that is, in activating a latent tuberculosis.

With regard to measles, it is well known that there is a relation between latent tuberculosis and measles. I think that it is hardly justifiable to say that whooping cough activates a latent tuberculosis as measles may. I occasionally see a case of miliary tuberculosis following whooping cough, but the total number of such cases is so small that I think one would not be justified in saying there was a definite relation.

I should like to ask whether these reactions showed any difference at different seasons, whether the same patient tested at different seasons of the year showed a different reaction. That has already been noted, and I think that it is an interesting point, because the susceptibility to infection does vary at different times of the year.

DR. BÉLA SCHICK, New York: I was much interested in the facts Dr. Mitchell brought out. As far as the tuberculin reaction is concerned, I always found in measles about the same results as Dr. Mitchell.

I remember a paper of Dr. Gruener in which he stated that the sensitiveness of tuberculin during the measles process is diminished about 100 times. This means that in the acute state of measles (from one to five days after the commencement of the eruption) a positive reaction is obtained with 1 mg. of old tuberculin, injected subcutaneously or intracutaneously. The difference in the sensitiveness is also occasionally true for active febrile cases, especially in pneumonia. The difficulty in deciding whether the sensitiveness is really lowered or not lies in the fact that the reaction must be repeated in the same person. It is known that in repeating the injection of tuberculin the second reaction can be intensified by the first. A negative Pirquet reaction may be obtained the first time a child with an inactive tuberculous condition is tested. When the test is repeated after fourteen days, the second test is frequently positive. If instead of a cutaneous test, one would inject 1 mg. of tuberculin, one would obtain a general reaction.

As far as the diphtheria toxin reaction is concerned, I tried to study it in measles and in other diseases. I did not find any marked difference in the intensity of the reaction.

I wish to mention one fact which apparently is not so well known; that is, the parareaction (pseudoreaction) after diphtheria. After diphtheria it is easier to get the parareaction (pseudoreaction), which apparently is due to some specific substances in the diphtheria toxin solution. Furthermore, there is a parallelism

between the intensity of the reaction of tuberculous persons against different toxins, dysenteriatoxin, diphtheria toxin, colitoxin. I explained this several years ago by the theory that apparently the mechanism of the inflammatory reaction is about the same in the different toxins.

I think that the observations of Dr. Mitchell should be further studied on a larger scale.

EPIDEMIC PEMPHIGUS OF THE NEWLY-BORN. DR. FRANK C. NEFF.

Not any statistics and only a few reports of epidemics of pemphigus in the United States have been published. A hospital contagion is a menace to all the infants as well as a serious problem for maternity departments. The occurrence of outbreaks at one of the hospitals in Kansas City is described, there having been from sixteen to twenty-three cases each during the past three years. The disease has been mild, and with a few exceptions fever or disturbance in the progress of weight of the infants has not occurred. The lesions appeared from the third to the eleventh day of life, the sixth day, on the average. During 1927, twelve of the twenty-three infants were well when leaving the nursery. Not all infants in the nursery during the epidemic contracted the infection.

For the prompt recognition of the disease and avoidance of an epidemic, the attendants should be daily on the lookout for the appearance of a bulla. The evolution of the lesion and the course of the mild and severe cases are described. Pemphigus may be limited to one vesicle or to a single group. A fatal outcome occurred in an infant that first had a typically mild course, followed by the sudden appearance of numerous widespread bullae which became confluent and resulted in generalized exfoliative dermatitis, accompanied by high temperature and terminating by sepsis.

The pathogenicity of *Staphylococcus pyogenes aureus* usually found in the early stage of the lesion is as yet not universally acknowledged, but is suggested by its frequent presence in pure culture and its occurrence in lesions produced by inoculation. That the source may be from the mother's milk or from the use of irritating antiseptics are theories worth further study.

The methods of transmission to the infant or from patient to patient are described. The infection may be carried to older infants and adults. That the disease is a clinical entity is proved by the type of lesion and by its predilection for the newly-born. In spite of the fact that pemphigus is usually mild, a considerable number of fatalities occurs.

In the treatment, the prevention of an epidemic is more important than the local applications, as the course is usually self-limited. Recently the nursery has been using Milian's lotion which consists of brilliant green, crystal violet and alcohol. This is applied once or twice daily and apparently with favorable results. All other applications that are commonly used have not proved of value.

The establishment of aseptic nursing, such as is employed in contagious hospitals, will be of the most benefit. This means the exclusion of carriers and of the infected linen, the isolation of the infected infant and mother and the employment of an individual nurse.

DISCUSSION

DR. CLIFFORD G. GRULEE: I find that frequent applications of alcohol to the skin of these infants is the one thing that does good, and I doubt if putting solutions of green, red, yellow or blue into this alcohol makes much difference. I believe that a solution of 90 per cent alcohol should be used.

DR. CHARLES G. KERLEY: Epidemics such as the one described by Dr. Neff seem bound to occur now and then in the best managed obstetric wards. According to my observation, the best plan is to rupture the vesicle as soon as it begins to form and to saturate the vesicle area and the surrounding parts with pure alcohol. Following such treatment, the parts are kept moist with a saturated solution of boric acid, with frequent inspection for new vesicles.

DR. R. LANGLEY PORTER, San Francisco: I should like to ask Dr. Neff whether he has not met hospital attendants and obstetricians who left a trail of infection behind them, and why is it not more logical to exclude from contact with the children all attendants with chronic conditions of this sort?

DR. WALTER LESTER CARR, New York: In the past year, in a maternity hospital, there were sixty-five infants with impetigo. The lesions were scattered on the neck, face and different portions of the body. These cases started in the private nursery, and all the usual precautions were taken. The nurses wore gloves and the infants were quarantined. The walls and cribs were repainted. Alcohol proved the best local application. I stopped the bathing of the infants during the epidemic. By these methods a better result was obtained than in the early period of the epidemic when for a short time ammoniated mercury preparations were used.

When mothers were found with lesions around the nipple, the infants were not allowed to have the breast; the breasts were pumped, and the infants were given breast milk from the bottle. The mothers were satisfied so long as they felt that the infants were doing well. There was a slight rise of temperature in a few infants and not any deaths. Little general loss of weight occurred.

In lesions that were slow in healing, benefit was derived from the use of an incandescent bulb kept near the infant, as is done for burns, and it was effective in drying the skin.

The precautions I would take in another epidemic would be to isolate the infants; have the nurses wear gloves and not bathe the infants; use alcohol locally for the lesions and keep the skin as dry as possible.

DR. JOHN A. FOOTE, Washington, D. C.: This is, of course, a hand borne infection, distributed by physicians, nurses or attendants. The epidemic usually begins with one case, and is then passed on to noninfected infants. I am certain that some of these initial cases originate from infected secretion of the vagina or infected areas in the vulva. I know of two cases in which the lochia showed a great number of staphylococci and streptococci, and in one of them the glands of Bartholin were infected.

In many of the nurseries, especially in smaller hospitals, stationary wash stands are not available for use. The nurse or attendant is often obliged to leave the room in order to wash her hands. There is a great temptation under such conditions to go from one infant to another without taking the precaution of washing the hands. I believe that if stationary wash stands with running water were placed in sufficient number in all nurseries and proper technic enforced, fewer epidemics of this infectious disease would occur.

DR. DEWITT H. SHERMAN, Buffalo: It may not be important, but among the private cases in the Children's Hospital in Buffalo the routine now is the application of an ointment of 2 per cent ammoniated mercury and 2 per cent mild mercurous chloride in petrolatum. It is applied the first and third day and also on the day before the child is discharged. Since this routine has been established, not any cases have occurred, but I am apologetic in speaking of it, since this treatment has not been in use for many months.

DR. G. RAYMOND HOOBLER, Detroit: Epidemics of this disease have occurred in the maternity ward of the Woman's Hospital. Not until a basin of lysol, with rubber gloves and gowns for every attending obstetrician and pediatrician to use in coming into the hospital was placed at the entrance of the hospital was it possible to eradicate the epidemic from the hospital wards.

I believe that in this particular instance the infection was carried on the hands of either the pediatrician or the obstetrician. I am sure that in this instance, at any rate, the disease was eradicated by establishing the precautions for the attending physicians.

DR. LAWRENCE T. ROYSTER, University, Va.: I should like to bring out one point that is interesting from the standpoint of spread. At the University of Virginia Hospital the new-born infants are under the care of the pediatric department just as soon as the cord is cut. As nearly absolute control is had over the patients in the wards as can be had with the facilities, and less control is had over the patients in private rooms. Several mild outbreaks have occurred in the last four years—in one instance as many as four at one time, but in most instances one or two. They have with one exception originated with infants in private rooms.

It seemed that this was due to the fact that the number of visitors in the private rooms were not allowed in the wards. The patients in private rooms demand visitors, and it is hard for the visitors to keep their hands off the babies. In every instance the lesions on the face were transmitted by visitors to private rooms, and only when visitors were forbidden entrance to the room at the time of nursing were these infections stopped.

DR. NEFF: Several of the points mentioned in the discussion are considered in my paper, but were not read because of lack of time. In regard to Milian's solution, about which Dr. Grulee spoke, I think it is not at all improbable that the alcohol is the chief effective part of the prescription. I was led to begin the use of this alcoholic solution of the dyes by the favorable reports of Sauphar abroad. Sauphar felt that the effect on the lesions was almost instantaneous. From a considerable experience I do not think that it is as rapid as that, but it has given better results than anything else that has been used.

I do not believe that the obstetrician is to blame for spreading the disease in the hospitals with which I am acquainted, for he is careful and practices asepsis, always wearing gloves. After the initial case many of the others result from contamination in the nursery, but some may come from the source of the original infection. In one instance the infection evidently spread from a mother who had pustular lesions on the hands.

FURTHER OBSERVATIONS ON CELIAC DISEASE. DR. CHARLES GILMORE KERLEY.

In 1924 I reported fifteen cases of celiac disease before this society. Gee Still, John Thomson and other earlier writers claim that dwarfism is often an end-result in cases in which recovery occurs: In eight of the fifteen patients of whom I was able to gather information to date, the results of growth are as follows: Three are from 2 to 4 inches (5 to 10.16 cm.) overheight for their age. Two are of average height and three are under height—one 1 inch (2.5 cm.), one 2½ inches (6.2 cm.) and one, 4 inches (10.16 cm.). In the two that are markedly underheight, the illness was of long duration—from two to three years.

The disease is manifested by marked muscle atrophy, failure of growth and copious, loose stools of an acid, decidedly foul odor, and general feebleness, and is to be classified as a disease caused by protein deficiency.

The use of cow's milk in all forms, including dry and fluid protein milk, has been so unsatisfactory that a casein product has been substituted which is combined with starch and sugar as follows:

Casein	2¼ ounces (69.9 Gm.) (sodium caseinate)
Starch	2¼ ounces (baked barley flour)
Sugar	2¼ ounces (cane, lactose or karo)
Water	30 ounces (887.2 cc.)

The barley is cooked for one half hour, and sugar is added at the completion of the cooking. The sodium caseinate is soluble in water, a solution is made and added to the barley sugar mixture when cool.

Analysis of the casein by the French Pancoast Laboratories is as follows:

Moisture	8.42
Fat	0.43
Protein	81.47
Ash	5.71
Lactose	3.78

A 20 pound (9 Kg.) child taking 30 ounces daily of the casein mixture would receive 43 grains (2.8 Gm.) of protein per pound of body weight and sufficient ash to insure the utilization of the protein.

The celiac child will assimilate starch and sugar in moderate amounts, if cow's milk in all forms is eliminated. For the first few days the casein, starch and sugar mixture is given plain or if not readily taken it may be flavored with cocoa, coffee or otherwise together with 1 drachm (3.75 cc.) of sherry wine at two hour intervals. The later diet consists of ground red meat, ground white meat of chicken, gelatin with orange juice flavoring, yolk of powdered hard boiled egg, bananas and bread crusts.

A decoction containing the vegetables, potato, carrots, turnip and celery is given at different times during the day for the purpose of supplying vitamin B, in which the foregoing diet is deficient. The first sign of improvement is a happier disposition, a tendency to play and improvement in the stools. A bismuth preparation and powder of ipecac and opium are given if the diarrheal stools are not controlled. A brief résumé of the cases reported is as follows:

	Present Age	Weight, Pounds	Height, Inches	Lowest Weight, Pounds	and Age, Months
1.	5 years 2 months	38¾	42½	20	29
2.	3 years 9 months	36⅞	38⅝	21	30
3.	4 years 4 months	35¾	37½	19½	31
4.	3 years	38⅜	35	16	21
5.	5 years	34½	36⅞	23	30
6.	7 years 3 months	46½	45	17¾	22

In three months patients 1 and 3 gained 7 and 7¼ pounds (3,175.14 and 3,288.54 Gm.) respectively. In three months patient 2 gained 5½ pounds (3,494.7 Gm.). In five months patient 4 gained 10 pounds (4,535.9 Gm.).

Patient 5 refused casein milk, but when given protein in different forms made a slow gain—11½ pounds (5,216.3 Gm.) in thirty months.

Patient 6 gained only 12 ounces (340.2 Gm.) in nineteen months; the child was kept alive on casein milk and could take little other food; in nine months, the patient gained 9¾ pounds (4,422.5 Gm.); the later gain was satisfactory. The success in the management of cases 1, 2, 3, 4 and 6 is attributed to the complete withdrawal of cow's milk, the substitution of an assimilable protein in adequate amount and in careful selection and adjustment of the carbohydrates with due respect to the vitamin content of the diet.

DISCUSSION

Dr. F. F. Tisdall, Toronto: Has Dr. Kerley any theories as to the cause of this condition? Also, has he any reason for his statement that milk is bad, and

why? I have thought that sugar and starch caused the trouble and not milk. He has rather turned this conception upside down. I should like to get further information about his theory.

Dr. Alfred F. Hess, New York: Infection should be emphasized in connection with these cases. I feel that to avoid infection is most important. If one can prevent the patients from having fever one probably can pull them through. Furthermore, as a corollary, the prognosis is much better in the spring or the summer, when there is little infection, than in the autumn or the winter. I suppose Dr. Kerley has had similar experiences.

Dr. Kerley: I wish to emphasize that the cases that I have shown were true celiac cases as described by Gee and not simply an aggravated form of chronic intestinal indigestion. There is a distinct difference between the two conditions. I have perhaps twenty-five patients with celiac disease under my care at the present time and many more with chronic intestinal indigestion. In celiac disease I omit milk in all forms, as I could not get satisfactory results with it. In chronic intestinal indigestion, mucous colitis and such diseases, protein milk does well and here I do not use the powdered protein milks or the Finkelstein Eiweiss-milk but a product made from the evaporated milk which is cultured two hours, thus obviating the acid taste which is objectionable to many children. This milk is as effective from a digestive and nutritional standpoint.

In celiac disease the casein-starch-sugar mixture supplies feedings of reasonably high caloric value; the casein is readily digested and a burden is not added to the child as is the case with the milk products. The mixture may be made palatable in different ways as has already been suggested and when one adds orange juice, vegetable decoctions, banana, powdered egg yolk and rare meat, one supplies a feeding plan that is working out more satisfactorily than any other means that I have been able to employ.

Moving Pictures of the Results of Injury of the Central Nervous System at Different Levels, Showing Physiologic Mechanisms. Dr. Bronson Crothers and Dr. Randolph K. Byers.

The central nervous system can be injured at birth in any one of a number of ways. Direct injury by traction or distortion is the easiest to understand and to prove. Asphyxia and hemorrhagic disease are less clean cut and more open to question. The obvious effect of excessive traction is rupture, complete or partial, of the spinal cord or avulsion from it of spinal roots. The rupture of the dural septums may be accompanied by bleeding from various venous channels.

The patients shown were all subjected to severe strain during labor. Three were breech extractions, and the fourth was born after severe traction with an anteroposterior application of the forceps with a scar over the forehead still visible after six years. In each case the evidence is complete that mentality is normal. Convulsions have not occurred in any. The physiologic residue, therefore, in each case is sufficient to justify efforts at salvage. In these subcortical injuries we believe that physiologic rather than conventional neurologic technic reveals the physiologic situation.

Four films were shown:

Film 1.—A boy, aged 2 years, delivered by breech extraction, showed complete flaccidity of the legs with total anesthesia and automatic sphincters. The lower spine was dislocated. Bilateral inguinal hernias and a postnatal spontaneous fracture of one femur were present. Reflex activity had been previously noted. The present situation points to a total destruction of the lower cord.

FILM 2.—A girl, aged 6 years, likewise delivered by breech extraction, showed marked hyperesthesia below the chest, feeble voluntary movements of the legs and strong contractions of the legs on nocuous stimulation. Increased reflexes or contractures were not noted. The sphincters were automatic.

Here a midthoracic transection, almost complete, is assumed. Obviously a few fibers were still intact, resulting in the feeble movements, but the child showed essentially the physiologic picture seen after sharp transection in the thoracic region.

FILM 3.—A girl, aged 5 years, also delivered by version extraction, showed weakness, ataxia and scoliosis, apparently due to a diffuse subtotal injury of the thoracic cord.

FILM 4.—A boy, aged 6 years, born by a difficult forceps delivery, showed a clinical picture dominated by dystonia and chaotic extrapyramidal disturbances. In addition, a flaccid one-sided facial palsy existed.

In this case intracranial stress due to traction with the blades of the forceps over the occiput and face may be assumed. A rupture of the dural septums with bleeding or thrombosis of tributaries of the vein of Galen might easily produce cellular damage in the striatal region.

The conventional description of cerebral palsy as a condition affecting the mind and the pyramidal tracts seems to us mischievous and inaccurate. We believe that an unprejudiced survey of these children will reveal many with neither difficulty. The salvage of those with normal mentality depends on an adequate realization of the physiologic disturbances involved.

DISCUSSION

DR. CROTHERS: I do not think that I can add anything except to emphasize that giving up these children without trying to make a physiologic diagnosis seems to me rather unreasonable. The condition of the last child shown has been diagnosed in many ways. The family started to California; on the way, they were advised and told many things—from the child being an idiot to the necessity for a craniotomy to relieve the increased cranial pressure. As far as I know, education was the last thing anyone was interested in, instead of the first.

DIFFERENTIAL DIAGNOSIS OF THE PNEUMONIAS IN CHILDHOOD. DR. CHARLES HENDEE SMITH and DR. ALFRED G. LANGMANN.

From a study of clinical cases, roentgenograms and material obtained at autopsy in persons with pneumonia, we have found several distinct types of disease.

Lobar Pneumonia.—Lobar pneumonia exactly resembles that seen in adults and older children and occurs in infants and young children more commonly than any other pneumonia. It has a sudden onset, high fever (regular or fluctuating), a sharp crisis, and usually physical signs of consolidation. The shadow on the roentgenogram is sharp, dense and homogeneous and is wedgeshaped in the upper lobes and variable in shape in the lower. The sputum contains pneumococci. The pathologic condition is that of adult lobar pneumonia. Since the mortality is low, this condition is rarely found at autopsy, but it does occur.

Bronchopneumonia ("lobular," catarrhal, secondary) is a term used to cover several different entities. The cases we have studied fall into certain definite groups.

2. *Peribronchial Pneumonia, or True Bronchopneumonia.*—The lesion is an infiltration with lymphocytes of the submucosa of the smaller bronchi. A patchy

consolidation of some adjacent alveoli is also found. The exudate is poor in fibrin and consists mostly of desquamated epithelium.. There are usually many collapsed alveoli. The bases and posterior portions are mostly involved. Dilatation of many infundibula and alveoli, especially along the anterior border of the lung, is found.

This occurs as a primary disease after a simple respiratory infection or after infectious disease (such as measles or pertussis), or as a terminal event in marasmus, or any slowly fatal condition. The clinical course varies from a mild illness with moderate prostration and recovery by lysis to a severe or prolonged and frequently fatal disease. In these forms there is extreme prostration and real dyspnea, not merely rapid breathing. Resonant or consonating râles are the characteristic physical sign and the only one present in the milder cases, but there may be signs of consolidation.

The roentgenogram does not show a shadow even when there are physical signs of massive consolidation and a pseudolobar involvement at autopsy. In long standing cases there may be a fraying out of the hilum markings. Occasionally massive atelectatic areas cast a shadow. The failure of this peribronchial pneumonia to cast a shadow is not readily explained. It may be due to the few leukocytes and scanty fibrin content of the exudate or, as Duken believes, to obscuring of the shadow by the increased air content of the dilated infundibula.

The organism found is usually a streptococcus, and the mortality is high.

3. *Lobular Pneumonia.*—Lobular pneumonia occurs as a primary disease, or after aspiration of food, gastric contents, or other irritating or infected substances (liquor amnii) and often follows influenza. In this the lesion is an acute exudation into some of the lobules of the lung, as if the infection had traversed the lumen of the bronchi and entered the alveoli by this route. There is patchy consolidation, which corresponds more or less to the anatomy of the lobules. The exudate contains considerable fibrin, many leukocytes, some desquamated cells, and often many red cells. The amount of each varies greatly in adjacent lobules or in different parts of the same lobule. A tendency to focal abscesses and necrosis often occurs. The bronchi in the involved areas contain many leukocytes, but a peribronchial collar of lymphocytes is not present. In the influenzal form and in the diffuse congenital pneumonia due to aspiration of infected liquor amnii, there is seen in places a hyaline degeneration of the lining of the bronchioles and alveolar ducts. This is a definite, though greatly varied pathologic picture, different from the peribronchial form. The bacteriology is varied; streptococci, pneumococci and influenza bacilli are found.

The clinical course is usually prolonged with severe general symptoms, high irregular fever and lysis if recovery takes place. The physical signs resemble those of bronchopneumonia—resonant râles or signs of consolidation over the involved lobes.

The roentgenographic shadow in the lobular pneumonias varies. In some cases it appears as a patchy or mottled area resembling tuberculosis, which spreads to a diffuse shadow but still is not homogeneous. In other cases, a shadow is not seen at first but one gradually appears after several days at the hilum or apex and slowly spreads over the pulmonary field. At times a shadow indistinguishable from lobar pneumonia may appear at some one stage of the disease.

4. *Interstitial Pneumonia.*—The characteristic of interstitial pneumonia is an enormous distention of the lymphatics of the interlobular connection tissue septums by large numbers of leukocytes. The pleura is usually involved and this condition has been called pleurogenous pneumonia, because the septums extending in from

the pleura are most inflamed. The lung gives physical signs of consolidation, is deep red and appears solid; microscopically, there is little if any exudate into the alveoli but merely collapse and acute congestion. A hemolytic streptococcus was found.

5. *Mixed Forms.*—The finding of mixed forms confuses the matter and is responsible for the lack of clearness in the descriptions in textbooks. Many cases are definitely lobular, but there is a peribronchial pneumonia elsewhere in the lung and some of the bronchi in the confluent lobular areas show a true peribronchial collar. The simultaneous occurrence of an acute interstitial lesion with bronchopneumonia was seen in the postmeasles cases in the 1918 epidemic, and Macallum called this "acute interstitial bronchopneumonia." Lobar pneumonia in the upper lobes may be accompanied by peribronchial pneumonia in the lower. In one case in which the condition was definitely lobular, the patient seemed to develop a lobar type in the upper lobes just before death. If these different lesions are merely tissue reactions to different infecting agents it is to be expected that mixed infections will give mixed lesions. It is important that in most of the fatal cases of mixed forms the patients have been sick for many days before death, and have probably developed bronchopneumonia just as in any other slowly fatal disease. If any patient who is going to die lives long enough, he will develop bronchopneumonia.

The foregoing classification is one we have arrived at by a study of our own material but is supported by Kauffmann (Special Pathology). We think that a careful study of each case clinically and repeated roentgen-ray examination should enable us to predict more accurately what the autopsy will show. The matter is important on account of the prognosis, which is good in the lobar form and distinctly bad in bronchopneumonia and lobular pneumonia.

DISCUSSION

Dr. Henry Heiman, New York: I noticed under the classification that Dr. Smith gave he mentioned the bronchial pneumonia type and the lobular type, but I believe the peribronchial infiltration deserves a place per se.

In the paper that I presented here last year, I spoke about the postinfluenza peribronchial infiltration. Examination shows that the percussion is the most important symptom of this condition. And so it should be, if the pathologic diagnosis that was given more than forty years ago by Field and more recently by McCollum is true. If peribronchial infiltration is present, one cannot expect to find râles because the air vesicles are free and clear, so all that is heard on auscultation is the dulness.

The greatest difficulty has been experienced, at the bedside at least, in the last few years in convincing most of the men, not students but even practitioners, that a condition which simulates an interstitial bronchial pneumonia is being dealt with, and that it is natural that these conditions will take much longer to resolve if one only reflects on the pathologic condition which exists there. In fact, I went a step further and postulated, at the time, that this peribronchial infiltration was a focus of infection, and that this is why these children get frequent colds of the upper respiratory refraction. This is new with roentgenologists. One cannot expect a shadow of the alveoli, but one does see, as they have put it, exaggerated stria. I also find, frequently (and I have viewed them in a great many cases of which Dr. Smith spoke), the conditions of which he spoke, but I do not classify them as lobar or lobular. These exaggerated stria are important when they are seen as far as the axilla. Only peribronchial infiltration will cause them.

DR. SMITH: The whole discussion of everything of this sort depends entirely on the definitions. I attended a meeting in Philadelphia last year on the definitions in tuberculosis. We talked for five hours, no one agreed about any definition. The same is true of pneumonia. One physician uses the term "interstitial" and one has to say, "What do you mean?" Another says bronchopneumonia, and one has to say, "What do you mean?" I think Dr. Richard Smith is right. An interstitial pneumonia heals and leaves a scar. I think the few cases of pure acute interstitial pneumonia that we have had have been fatal. But a peribronchial pneumonia is frequently followed by peribronchial fibrosis, and that is the chronic thing. It is not primarily a chronic pneumonia, but a chronic peribronchial fibrosis.

In textbooks on pathology and pediatrics, influenzal pneumonia is classified with bronchopneumonia in some cases; in others it is described as a special type. It seems to me that it belongs with the lobular types. When the hyaline degeneration of the lining of the alveoli which is found in a classic case is present, there is usually a lobular distribution of the exudate, not a peribronchial pneumonia.

I cannot agree with Dr. Heiman that fibrosis is common following influenzal pneumonia. In 1918, when thousands were in the hospital wards, an effort was made to follow as many as possible, and in not a single instance was late fibrosis found after severe influenzal pneumonia. I cannot help feeling that a true bronchopneumonia with a peribronchial collar of lymphocytic infiltration is more liable to be followed by a fibrosis than is the lobular influenzal pneumonia even when more marked peribronchial changes are present.

(*To be continued*)

NEW YORK ACADEMY OF MEDICINE
SECTION OF PEDIATRICS

STAFFORD MCLEAN, M.D., *Chairman*

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Clinical Meeting, May 10, 1928

TWO CASES OF ENDEMIC MENINGOCOCCUS MENINGITIS IN ONE FAMILY; LONG INTERVAL BETWEEN CASES; CARRIER. DR. STAFFORD MCLEAN.

Rocco Gaspari, aged 13 months, was admitted to the Babies' Hospital on Nov. 9, 1926, and was discharged cured on Nov. 18, The chief complaints were drowsiness, fever and vomiting three days with convulsions at the onset. Physical examination revealed, in addition to other signs of the disease, numerous fine petechiae on the lower extremities. Meningococci were obtained from the purulent cerebrospinal fluid in both smear and culture. The child was treated intensively with antimeningococcus serum intravenously and intrathecally and responded favorably to specific therapy. Nine days after admission he was discharged cured.

Joseph Gaspari, a nursing infant, aged 3½ months, the youngest child in the same family, one year later, Nov. 2, 1927, was admitted with a history of unexplained irritability of twenty-four hours' duration. Meningococci were obtained in smear and culture from the purulent cerebrospinal fluid. This patient also responded to similar treatment and was discharged cured seventeen days after admission.

The admission of the second child with the same disease, who was born eight months after the discharge of the first patient, suggested the presence of a meningococcus carrier in the household. The family included mother and father

and five children—aged 5, 4, 3 and 2 years, and 3½ months of age, respectively, and an aunt 16 years of age. Rocco, the infant who had had meningitis at 13 months of age, and Paul, aged 5, who had not had the disease, showed a positive culture for meningococci on swabs from the nasopharynx. The father and mother, the aunt, and two children, aged 3 and 5, showed negative cultures. This history presents three rather interesting points of the carrier problem:

1. The child harbored meningococci twelve months after convalescence from the disease.

2. The older boy harbored the organisms for an indefinite time and may have been the original source of infection in both children.

3. An infant from birth in close contact with at least one carrier of meningococci did not contract the disease until the age of 3½ months. (The Gaspari family of eight members lived in extremely crowded quarters in the slums. All five children were at the most susceptible age period for the disease.)

DISCUSSION

DR. MAY: There is a decided increase in the number of cases of meningococcus meningitis in town just now, though hardly enough to be called epidemic. The Bellevue pediatric service has been having many more cases than for some years, and the type has been a little different from the usual sporadic case. If cultures were made from the parents and others in the families of these children, one would probably find a good many carriers. This condition was found to exist at Camp Bowie in Texas during the war, when there was an outbreak of epidemic meningitis in the 32nd division. A survey of all those who had come into contact with the patients and of some whole companies was made by nasopharyngeal cultures. The carriers were isolated in hospital tents and held until four successive negative cultures had been obtained before being returned to duty. There were several hundred of these men, otherwise perfectly well. I remember that the most effective treatment for clearing up the condition at this time seemed to be spraying and gargling with chlorazine and a compound solution of sodium borate.

A CASE OF STREPTOCOCCUS MENINGITIS WITH RECOVERY. DR. LANG.

A boy, aged 2, was admitted to the Babies' Hospital with a negative family history; he had never been ill before. He had been nursed for seven months. The present illness began abruptly five weeks before admission, with fever (104.5 F.) and sore throat, which persisted. A diagnosis of scarlet fever without a rash was made, and antitoxin was given. The child was sent to Riverside Hospital, where he stayed two days and was then sent home as "no case." Restlessness, constant crying, refusal of food and loss of weight were prominent symptoms during the first five weeks of the illness. Two lumbar punctures and a blood culture gave negative results. Both ears were incised and discharged freely.

Physical examination showed a well developed, white, male child acutely ill, with a temperature of 102 F. and extreme irritability. The fontanel was closed and the neck rigid; right internal strabismus and tache were present, and the Kernig and Brudzinski signs were positive.

Lumbar puncture on admission showed cloudy fluid with 1,100 cells, 99 per cent of which were polymorphonuclears. Globulin was present and sugar absent. Gram-positive cocci in chains were found in spreads made from the fluid, and cultures grew *Streptococcus hemolyticus*. Quantitative chemical tests revealed: sugar, 19 mg. per hundred cubic centimeters; chlorides, 675 mg. per hundred cubic centimeters and blood sugar, 101 mg. per hundred cubic centimeters.

Examination of the blood showed: 2,528,000 red cells, 30 per cent hemoglobin and 13,000 leukocytes with 79 per cent polymorphonuclears. The urine contained a small amount of albumin, but was otherwise normal.

Antimeningococcus serum was given at the onset, with a resulting rise in the cell count. Scarlatinal antitoxin was then given intraspinously and intravenously (seven doses), causing a gradual rise in the spinal fluid cell count to 12,000. With cessation of treatment, the cell count gradually diminished to 2,500. The spinal fluid sugar remained below 20 mg. The child was given two blood transfusions, and the spinal fluid cultures were positive for *Streptococcus hemolyticus* on three different occasions.

The child lost weight, from 11,396 Gm. on admission to 8,900 Gm. on discharge, when he recognized his mother and took notice of his surroundings.

At present at the age of 4, he is well grown and well nourished, but mentally subnormal. He still has attacks of irritability. Cases of *Streptococcus hemolyticus* in which the patient recovers are still so few as to make the record of interest. Whether the meningitis and the primary illness were due to the same strain of streptococcus (scarlatinal) has not been proved.

HYPERTHYROIDSIM. DR. ABBOTT WINOGRAD.

D. S., a girl, aged 7 years, entered Mount Sinai Hospital on April 9, 1928, with a history of exophthalmos, and increasing nervousness dating back to May, 1927. On entrance, the child presented the clinical features of exophthalmic goiter, tachycardia, a pulse rate of 120 per minute, a fine tremor of the hands, hyperanxiousness, flushed cheeks and warm, moist hands. The thyroid gland was spongy and somewhat enlarged, the right lobe being larger than the left.

The basal metabolism on admission was practically normal, plus 6 per cent. On April 22, however, it was plus 27 per cent. On April 24, it was plus 28 per cent. Exophthalmometer reading was right eye, 21 mm.; left eye, 25.5 mm. The cholesterol content was 168 mg. per hundred cubic centimeters. The blood pressure was 124 systolic and 70 diastolic. Among the possible foci of infection, the tonsils were enlarged and cryptic, and a x-ray picture of the sinuses showed clouding of both antrums, more marked on the left, with thickening of the walls.

The child has not shown any change in her condition during her stay in the hospital. She has been on a high caloric diet, and her weight has been maintained. Owing to incidental infection in the upper respiratory tract, further treatment has not yet been carried out.

A CASE OF TUBERCULOSIS OF THE MEDIASTINAL LYMPH NODES IN AN INFANT ASSOCIATED WITH SCROFULODERMA AND TUBERCULOUS DACTYLITIS. DR. ALFRED G. LANGMANN.

A negro boy was admitted to Bellevue Hospital on April 18, 1927, at the age of 1 year with the history that since his discharge from Harlem Hospital three weeks before he had been coughing and having fever, as well as refusing food and losing weight. He had been at Harlem Hospital for two weeks with pneumonia. His family and birth history were reported normal, and he had been well up to the present illness.

Examination showed a moderately ill negro boy weighing a little over 15 pounds (6.8 Kg.). There were signs of moderate rickets. His breathing was somewhat accelerated, but not labored. His posterior pharynx was filled with mucus, and he had difficulty in swallowing semisolid food. The tonsils were moderately large. The tonsillar and posterior cervical lymph nodes were palpable, but there was no generalized enlargement of the lymph node. Over the lower lobe of the right lung posteriorly, there was dulness merging into flatness at the base. The breath sounds over this area were diminished and of a vesicular type, except over the upper portion of this lobe as well as over the upper lobe, where soft bronchial breathing was heard. Râles were not heard. The left lung appeared normal, and the heart did not show abnormal sounds and did not appear to be displaced. No definite substernal dulness could be determined. Both the liver and the spleen were slightly enlarged.

On these observations, the diagnoses of unresolved pneumonia with probable pleural effusion was made. The white blood count was 9,100 with 28 per cent polymorphonuclears, hemoglobin 54 per cent and a red blood count of 3,800,000; the appearance of the cells was normal. The intradermal tuberculin test was strongly positive. The temperature on admission was 100 F., and for the next three weeks it fluctuated between 100 and 103 F.

Repeated examinations of the sputum for tubercle bacilli were negative.

The day after admission, a thoracentesis was performed just below the angle of the right scapula, and 10 cc. of thin yellow pus was aspirated; culture of this was negative. Further aspirations were not made.

X-ray examination of the chest showed a rather dense shadow in the upper lobe of the right lung involving the mesial two thirds and also extending out to the periphery in the lower portion. There was a broad mediastinal shadow extending well into the left thoracic cavity and having a coarsely scalloped margin on this side; there was also evidence of a blanket effusion on the right side, extending from the apex to the base. X-ray examination of the extremities revealed a productive periostitis of the first and second metacarpals and one of the phalanges of the right hand.

About a month and a half after admission, several small papules about 3 mm. in diameter were noticed on the extensor surfaces of both forearms. The diagnosis of the dermatologists was lichen scrofuloderma.

At first it was suggested that the shadow in the mediastinum was probably caused by a new growth, possibly a lymphosarcoma, but the evidence was convincingly in favor of the shadow being due to tuberculous lymph nodes.

Three deep x-ray treatments were given, at weekly intervals. The child began to improve slowly though steadily, and now at 2 years of age he is in good general condition. X-ray examination of the chest shows only a slight widening of the mediastinal shadow.

Wassermann tests of both the blood and spinal fluid were negative.

A Case of Cardiospasm. Drs. Harry S. Mackler and E. Gordon Stoloff.

A boy, aged 8½ years, was admitted to the service of Dr. Schick at the Mount Sinai Hospital about four months before presentation with the complaint of vomiting for three years. The family history was irrelevant except that the father was extremely neurotic; the mother had died of heart disease. The patient had been a seven months' premature infant, and weighed 4½ pounds (2.05 Kg.) at birth. The past history was not pertinent except that he had had scarlet fever three years before presentation, following which he developed the vomiting for which he sought relief. The scarlet fever was mild, and during his convalescence the boy swallowed a large, iced confection which apparently stuck at the cardia, gave him epigastric cramps and was followed by vomiting. At first the vomiting occurred occasionally after eating; soon it became more frequent, and then almost invariably followed from a minute to five minutes after eating. He was able to retain small amounts of water, but not larger amounts; thick gruels were retained, but meats and coarse foods were not tolerated. A year before entry, he had a course of bougie treatments at the Lebanon Hospital without success. Shortly before admission, he was given atropine by mouth, which was fairly effective. He had lost about 5 pounds (2.3 Kg.) during the six months preceding entry.

Except for obvious undernutrition and underdevelopment and moderately dilated pupils incidental to mydriasis, the results of physical examination were negative. Esophagoscopy was performed by Dr. Yankauer: the tube was passed with ease into the stomach, and no lesions of any kind were found. Fluoroscopy revealed a markedly spastic condition of the esophagus in the upper third and at the cardia, with the typical regular dilatation above tapering down regularly and a constriction below.

For two weeks he was on a course of papaverine, 20 mg., and atropine sulphate, 0.3 mg., three times a day by mouth, before eating. In the main, there was no

vomiting, and the child gained about 2 pounds (0.9 Kg.) in weight on a liberal soft diet. He was then given the same dosage of papaverine and atropine hypodermically for another two weeks, during which there was no vomiting; and he gained about 4 pounds (1.8 Kg.) in all. The papaverine was then discontinued; the atropine was gradually reduced and then alternated with sterile hypodermics. The vomiting recurred. Fluoroscopy revealed a persistence of the cardiospasm. The patient was put back on atropine medication, 0.4 mg., three times a day before eating, and the vomiting again stopped. About two and a half weeks ago Dr. Burrill Crohn passed a Plummer hydrostatic esophageal dilator. There were no untoward reactions following the procedure. The patient has not been vomiting since, has been taking solids very well, and is gaining weight consistently. Fluoroscopy now reveals almost no spasm.

A more detailed report will be published.

DISCUSSION

DR. LEWALD: I have been much interested in cases of cardiospasm for some time. A girl of the same age as the patient whose case has been reported was brought to me by the late Dr. Pisek, and I had another case in a boy, aged 12. At the Mayo Clinic, they have observed cases in children from about 8 to 10 years of age. Cardiospasm, as it is seen in the adult, probably begins at about this age, and the esophagus gradually becomes stretched until enormous dilatations occur later. I have seen cases in which attempts to relieve the condition with antispasmodics have been made, but unsuccessfully. Permanent cures are usually obtainable by forcible dilatation, preferably under direct control through the esophagoscope, using hydrostatic pressure as advocated by Dr. Plummer of the Mayo Clinic or mechanical stretching as advocated by Dr. Lerche of St. Paul.

A CASE OF UNDULANT FEVER. DR. SAMUEL Z. LEVINE.

A girl, aged 2½ years, entered the New York Nursery and Child's Hospital on Feb. 25, 1928, for the third time in the past six months with fever and migrating joint pains and swellings. On all occasions, administration of salicylates was accompanied by a subsidence of the fever and involvement of the joints within a few days following admission. Except for undernutrition (weight 23 pounds [10.4 Kg.]), pallor, enlarged tonsils and a red, tender and swollen right wrist and left ankle, the results of the physical examination were negative. The heart was apparently normal, and there were no subcutaneous nodules or other rheumatic manifestations. Tuberculin and Wassermann tests of the blood were negative.

On March 8 and again on March 15, after subsidence of joint involvement and fever, she received direct transfusions from her uncle and father, respectively, for a moderate secondary anemia (red blood cells, 3,200,000 and hemoglobin 47 per cent). Four hours later, her temperature rose abruptly to 104 F., and for the following month it was irregular, with alternating periods of pyrexia and apyrexia. The fever during the febrile periods showed daily fluctuations between 97 and 106 F. She became increasingly apathetic, and her spleen, which was not felt on admission, increased in size until it was palpable 5 cm. below the costal margin. On April 14, the temperature returned to normal, and it has remained normal up to the present time. The general condition of the patient has steadily improved, and the spleen has again receded. The white blood cells varied between 6,800 and 10,000, with the polymorphonuclear leukocytes ranging around 50 per cent. Repeated examinations of blood smears did not reveal any malarial parasites, and three blood cultures taken at the height of the fever were negative. Unfortunately, the blood cultures were discarded at the end of forty-eight hours. Agglutination tests with the blood serum of the patient against organisms of the typhoid, paratyphoid A and B, and the proteus group (Felix-Weil reaction) were all negative. The alternating periods of apyrexia and pyrexia led to a tentative diagnosis of undulant fever. The diagnosis was confirmed by tests with the serum of the patient against the melitensis-abortus group of organisms (antigen of *B. melitensis*

II — Theobald Smith). Agglutination occurred in dilutions up to 1280. These dilutions were considered diagnostic of a *B. abortus-B. melitensis* infection by Dr. Krumwiede in whose laboratory the tests were carried out. He believes that infections due to *Bacillus melitensis* and *Bacillus abortus* cannot be differentiated with certainty by serologic methods, including agglutination-absorption tests.

As to the source of infection in the patient, the blood serums of father, uncle, mother and the four remaining children in the family were all tested against the same strain of melitensis-abortus organisms (*B. melitensis* II — Theobald Smith), and except for the serum of the youngest child (aged 15 months), agglutination occurred in dilutions of 320 or higher in all of the subjects. Agglutinations in these high dilutions are generally regarded as good evidence of undulant fever, past or present. It seems probable that the entire family was infected at the same time from a common, but as yet undiscoverable, source, and that the transfusion was given at the time when a recrudescence of the fever was about to take place in the patient. None of the children had ever been outside of New York, nor had they ever received goat's milk in their diet. Furthermore, the patient had never eaten meat of porcine origin. In the absence of evidence of infection from these sources, the possibility remains that the bovine variety of *Bacillus abortus*, which is rarely infectious to the human host, may have been the source of infection in this family through the medium of unboiled cow's milk.

TWO CASES OF INFANTILE SCORBUTUS MISTAKEN FOR POLIOMYELITIS. DR. JESSE M. BULLOWA and DR. LEON T. LEWALD.

J. A. P., a colored infant, aged 14 months, was admitted to Willard Parker Hospital on Oct. 3, 1927, with a history of having been irritable and crying for five days. The child did not appear very ill. He was irritable when disturbed, fairly well nourished and rachitic. The fontanel was open, but not full; the neck showed slight voluntary rigidity. The child screamed when an attempt was made to obtain a Kernig sign, and the slightest manipulation of the legs and thighs was painful. There was apparently no paralysis. The knee jerks were active. The temperature was 100.2 F., the pulse rate, 122, and the respirations, 32. The next day the temperature reached 101 F., and became normal on the fourth day. There were only four teeth. The gums were discolored. The child lay for the most part with the knees flexed and drawn up. The inguinal glands on both sides were enlarged. There was a marked rachitic rosary. There was marked tenderness of the limbs, especially on the right side. The red blood count was 5,200,000; the white blood count, 13,600, and the hemoglobin content, 76 per cent. The diagnosis on admission was poliomyelitis.

The next morning an intern suggested a diagnosis of scurvy. An x-ray examination showed increase in the transverse diameter of the epiphyseal end of the long bones with irregularity of the distal ends, indicative of rickets. The child was discharged twelve days later, and another x-ray picture was taken. He was given a diet of whole milk, vegetables, 2 ounces (59.14 cc.) of orange juice and 2 drachms (7.39 cc.) of cod liver oil three times a day. He improved markedly under treatment. A lumbar puncture was not performed. In spite of the first negative x-ray picture, the diagnosis of scurvy was maintained. The x-ray examination made on the day of discharge showed a change in the long bones suggestive of subperiosteal hemorrhages of scorbutic origin associated with rickets.

A. R., a white baby, aged 7 months, was admitted on Sept. 23, 1927, with a history of having had fever, attacks of vomiting and a general rash for eight days. Both legs were said to have been paralyzed for three days. She lost 1 pound (0.5 Kg.) in a week, and was poorly nourished. Both thighs were everted and flaccid. The knee jerks were absent. The Kernig maneuver caused pain. There was no rigidity of the neck. There was a fine, erythematous rash. The temperature was 100 F., the pulse rate, 110.

The next day the temperature reached 104., and the pulse rate 138. The following day the temperature fell to 101 F., where it remained until the eighth day, after which it was normal. Lumbar puncture gave 8 cc. of clear fluid, with a slightly increased amount of mononuclear leukocytes. There was no organization in the spread of culture. The result of tests for albumin was plus one; for globulin, three plus; tests revealed 40 mg of protein; 57 mg. of sugar and 702 mg. of chloride, per hundred cubic centimeters. The next day some infiltration of both thighs was noted, especially on the right. The child was unable to sit. The knee jerks, achilles and abdominal reflexes were not obtainable on account of restlessness. Because of the flaccid lower extremities and absence of the knee jerk of the right side, the diagnosis of poliomyelitis was made. The child had frequent movements, with undigested food and mucus. The next day the knee jerks and achilles reflexes were obtained. Three days later, there was an infiltration of both thighs. The x-ray pictures taken following admission showed irregularity of the epiphyseal regions. The child had been placed on a lactic acid milk mixture and Karo, cereal and vegetables, and had improved. On the fifth day, the right knee jerk was again absent, and the diagnosis of poliomyelitis was still adhered to by the resident staff. On that day, the absent knee jerk on the right side and apparently flaccid paralysis led the attending and resident staff to regard the condition as of gastro-enteric origin. By the tenth day, the general condition was much improved: the enteritis had subsided. The right thigh was thicker than the left. The child steadily improved, and was discharged on the fifteenth day.

After a second x-ray examination about ten days later had shown organization and callous formation, and a diagnosis of scurvy had been made, the mother said that the child had received a teaspoonful of orange juice at times since her fourth month; she also stated that she had noticed a thickening of the legs for a week prior to admission to the hospital.

The interesting feature about these two cases is that in both the condition was scurvy which was mistaken for poliomyelitis, and the first x-ray examination made before the occurrence of subperiosteal hemorrhages and deposition of lime gave little assistance in arriving at the correct diagnosis, though it confirmed that diagnosis subsequently. In one of these cases we succeeded in obtaining an x-ray picture seven months later which showed complete ossification of the subperiosteal hemorrhages. The importance of a lack of an adequate amount of the anti-scorbutic vitamin is demonstrated, as well as the efficiency of that substance in effecting a cure when given in sufficient quantity.

Book Reviews

THE NEWER KNOWLEDGE OF BACTERIOLOGY. By EDWIN O. JORDAN and I. W. FALK. Price, $10.00. Pp. 1196. Chicago: University of Chicago Press, 1928.

The collection of articles comprising this valuable book is written by eighty-two eminent authorities in the field of bacteriology and immunology. Each author discusses subjects to which he has contributed scientific knowledge, giving his conclusions as well as a general review of the work accomplished during the last ten years. In including papers of opposite views, the editors have occasionally duplicated subjects for the sake of clarity in cases in which divergence of opinion is held. The purpose of the volume as explicitly set forth in the preface is . . . "to obtain authoritative reviews of topics in which at the present time interest is particularly keen or investigation most active. . . . It does not purport in any sense to be a textbook, nor does it pretend to be a comprehensive survey of the whole field." However, as a reference book for the student, teacher and investigator it is an intensely interesting collection of concise, well documented reviews, of such value to the bacteriologist as the current issues of "Physiological Reviews" are to the physiologist.

Each chapter consists of from ten to twenty pages; the book is illustrated and the author and subject index are adequate.

It would be impossible to list the chapters and authors in this limited space, or to do justice to all of the discussions. The wide interest of the book can be indicated by a survey of the general plan and it seems justifiable to mention the names of some of the many well known contributors.

The subject of immunity, including antigens, antibodies, toxins, antitoxins, phagocytes, tissue immunity, Aberhalden's reaction and venoms, including chemical aspects of these problems, takes up a large portion of the book, making twenty-three chapters. Among the writers of these chapters are H. Gideon Wells, Stanhope Bayne-Jones, Hans Zinsser and J. Howard Mueller, Frederick P. Gay, G. Howard Bailey, C. G. Bull and R. L. Kahn.

There are thirteen chapters on public health and commercial aspects ably treated by such men as Edwin O. Jordan, G. W. McCoy, Robert S. Breed, William H. Park and Milton J. Rosenau.

Another group of thirteen chapters deals with physical and chemical problems of bacteriology and immunology. I. S. Falk, Philip Hadley, William D. Harkins, Ivan C. Hall and W. Mansfield Clark are among the contributors.

Metabolism is treated in six chapters, one being written by James Walter McLeod, one by Arthur Isaac Kendall and one by Leo F. Rettger.

Chapters on anaphylaxis and allied subjects are by W. H. Manwaring, Howard T. Karsner and Arthur F. Coca.

Four chapters deal with soil bacteriology; three chapters in which are found the names of Noguichi, Hegner and Taliaferro deal with the blood and intestinal parasites of man, and two articles are on blood groups. There are chapters on bacterial morphology and classification, synthetic culture medium, communicable diseases in laboratory animals, elective localization of bacteria, intestinal bacteria, bacteria of the respiratory tract, yeasts and fungi, tuberculin, bacteriophage, chemotherapy and protein therapy.

DIE KLINSCHE HAEMATOLOGIE DES KINDESALTERS. By HEINRICH BAAR and EUGEN STRANSKY. Pp. 506. Price, 32 marks. Leipzig and Vienna: Franz Deuticke, 1928.

This is a most complete and exhaustive treatise on hematology in childhood and gives in detail not only the blood picture in various well recognized diseases of the blood, but prefaces this with an excellent discussion of the normal blood. All

the different types of blood dyscrasia are discussed in detail as well as the blood picture in infections and other general diseases. Splenomegaly, in its various forms, is well presented, and all the points in differentiation are brought out even to the latest literature on the subject.

The confusion in the knowledge concerning the various forms of anemia in early life cannot, however, be said to have been greatly benefited by the discussion of the subject; but at least all points of view are amply presented.

All the latest developments in hematology are given recognition, and a discussion and bibliography are included. This book should fill a long felt need as an excellent reference book on the subject.

THE PRINCIPLES OF ANTENATAL AND POSTNATAL CHILD HYGIENE. By W. M. FELDMAN, M.D., B.S., M.R.C.P. (London), F.R.S. (Edinburgh). Price, $7.00. Pp. 143. London: John Bale Sons & Danielsson, Ltd., 1927.

This book covers a wide range and contains a good theoretical discussion of the subject. The historical references are good, but one wonders in looking over the 100 portraits in the text just what some of the originals contributed to the subject.

All phases of child hygiene are discussed, beginning with the antenatal period. Nutrition and artificial and breast feeding are discussed at some length, as is also prematurity.

One of the best chapters is that devoted to heliotherapy.

The prevention of infectious disease is well discussed and controversial points are taken up exhaustively and are well illustrated.

The chapter on "Mental Hygiene of Early Life" treats a subject which is especially appealing at the present time.

The book is neither a practical treatise nor a reference book, but falls some place between the two.

MANUEL CLINIQUE ET THÉRAPEUTIC DE LA DIPHTHÉRIE. By P. LEREBOULLET and G. BOULANGER-PILET. Price, 40 francs. Pp. 321, with 49 figures, and 2 colored plates. Paris: J. B. Baillière et fils, 1928.

The book begins with a brief but complete résumé of the history of diphtheria, and then continues with the etiology and immunity of the organism. The clinical diagnosis is well discussed, with a complete description of the many lesions. As is usual in French textbooks, the bacteriology is well discussed and illustrated. The treatment also includes a full description of the methods of intubation, as well as the complications that may result from reactions to the serum. This book is complete, and the subject matter is easily accessible. The illustrations are drawings, but these are so simple that their meaning is made clearer than could possibly be done with photographs.

A BOOK FOR US DIABETICS. By DON H. DUFFIE, M.D. Price, $1.50. Pp. 80, with 12 illustrations and photographs. South Lancaster, Massachusetts: published by the Author, 1928.

This is a concise little volume giving briefly some clear and worth while information to the diabetic patient. It is divided into fifteen short chapters. The first seven chapters deal with the disease and methods for carrying on a home examination of the urine, with insulin treatment; the last seven deal with forms of diet. The book is well written, plainly printed, and the small illustrations are well chosen. It manages to put essential things in simple language.

L'IMMUNITE DU NOURRISSON. By GERMAINE DREYFUS-SEE. Pp. 194. Paris: Louis Arnette, 1928.

This is a discussion of the factors controlling the immunity of infants to disease. The subject is covered well for so small a book, and the conclusions are clearly stated.

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President: Dr. Paul W. Emerson, 86 Bay State Road, Boston.
Secretary: Dr. Ralph M. Tyson, 1527 Pine St., Philadelphia.
Place: Portland, Ore. Time: July 8-12, 1929.

AMERICAN CHILD HEALTH ASSOCIATION

President: Hon. Herbert Hoover, 370 Seventh Ave., New York.
Secretary: Dr. Philip Van Ingen, 370 Seventh Ave., New York.
Place: Stevens Hotel, Chicago. Time: October 15-19, 1928.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

President: Dr. G. R. Pirie, 20 Madison Ave., Toronto.
Secretary: Dr. A. P. Hart, 1844 Bloor St. West, Toronto.

SECTIONAL

CENTRAL STATES PEDIATRIC SOCIETY

President: Dr. H. T. Price, 121 University Place, Pittsburgh.
Secretary: Dr. A. H. Parmelee, 310 S. Michigan Ave., Chicago.
Place: Pittsburgh. Time: October 26-27, 1928.

SECTION ON PEDIATRICS OF SOUTHERN MEDICAL ASSOCIATION

Chairman: Dr. E. C. Mitchell, 1073 Madison Ave., Memphis, Tenn.
Secretary: Dr. A. J. Waring, De Renne Apts., Savannah, Ga.
Place: Asheville, N. C. Time: November 12-15, 1928.

LOCAL

NORTHERN CALIFORNIA PEDIATRIC SOCIETY

President: Dr. W. L. Channell, Medical Bldg., Oakland, Calif.
Secretary: J. E. Parrott, Medico-Dental Bldg., San Francisco.
Place: Various Teaching Schools. Time: Monthly.

SOUTHWESTERN PEDIATRIC SOCIETY

President: Dr. Oscar Reiss, Westlake Professional Bldg., Los Angeles.
Secretary: Dr. William Sidney Bowers, 1136 W. 6th St., Los Angeles.
Place: University Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

THE ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. W. Wiley Jones, Majestic Bldg., Denver.
Secretary: Dr. Berryman Green, 537 Republic Bldg., Denver.
Place: Children's Hospital, Denver. Time: Third Saturday of each month, 2:30 p. m., September to May, inclusive.

GEORGIA PEDIATRIC SOCIETY

President: Dr. Joseph Yampolsky, 127 Peachtree St., Atlanta.
Secretary: Nevin M. Atkins, Atlanta.

PEDIATRIC SECTION OF FULTON COUNTY MEDICAL SOCIETY, ATLANTA, GA.

President: Dr. William W. Anderson, 362 Peachtree St., Atlanta.
Secretary: Dr. Lee Bivings, Exchange Bldg., Atlanta.
Place: Academy of Medicine, 32 Howard St., Atlanta.
Time: Second Thursday of each month from October to April, at 8 p. m.

NEW ENGLAND PEDIATRIC SOCIETY

President: Dr. James Herbert Young, 66 Commonwealth Ave., Boston.
Secretary: Dr. Thomas Lanman, 286 Marlborough St., Boston.
Place: Boston Medical Library. Time: Second Friday of each month.

CHICAGO PEDIATRIC SOCIETY

President: Dr. Maurice Blatt, 30 N. Michigan Ave., Chicago.
Secretary: Dr. J. K. Calvin, 104 S. Michigan Ave., Chicago.
Place: City Club. Time: Third Tuesday of each month.

LOUISIANA STATE PEDIATRIC SOCIETY

President: Dr. L. R. De Buys, 1487 Delachaise St., New Orleans.
Secretary: Dr. F. J. Kinberger, 3601 Prytania St., New Orleans.

DETROIT PEDIATRIC SOCIETY

President: Dr. George E. White, Capitol Theatre Bldg., Windsor, Ontario, Canada.
Secretary: Dr. W. S. O'Donnell, 1563 David Whitney Bldg., Detroit.
Place: Children's Hospital of Michigan. Time: No fixed date; approximately once a month.

NORTHWESTERN PEDIATRIC SOCIETY

President: Dr. F. W. Schlutz, University of Minnesota, Minneapolis.
Secretary: Dr. E. S. Platou, 730 La Salle Bldg., Minneapolis.
Place: University Campus and Rochester. Time: Winter, Spring, Summer, Fall.

ST. LOUIS PEDIATRIC SOCIETY

President: Dr. Park J. White, Beaumont Bldg., St. Louis.
Secretary-Treasurer: Dr. Ralph L. Cook, 508 N. Grand Blvd., St. Louis.
Place: St. Louis Children's Hospital. Time: At least once a year and contingent thereafter on the arrangement of a suitable program.

NEBRASKA-IOWA PEDIATRIC SOCIETY

President: Dr. Floyd Clarke, 731 City Nat'l Bank Bldg., Omaha.
Secretary: Dr. R. B. Eldredge, 1036 Medical Arts Bldg., Omaha.
Place: Add-Sell Restaurant. Time: Second Thursday of each month from October to May, inclusive, 6 p. m.

BROOKLYN PEDIATRIC SOCIETY

President: Dr. Louis M. Ruderman, 961 Eastern Parkway, Brooklyn.
Secretary: Dr. Joseph F. Paulonis, 1357 Bushwick Ave., Brooklyn.
Place: Kings County Medical Society Bldg. Time: Last Wednesday of each month, except June, July and August.

BRONX PEDIATRIC SOCIETY

President: Dr. William Hinz, 1964 Grand Concourse, New York.
Secretary: L. H. Barenberg, 1749 Grand Concourse, New York.
Place: Concourse Plaza, 161st St. and Grand Concourse, New York.
Time: Second Wednesday of each month, except June, July, August and September.

CENTRAL NEW YORK PEDIATRIC CLUB

President: Dr. Frank Vander Bogert, 111 Union St., Schenectady, N. Y.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany, N. Y.
Place: Various Cities in New York. Time: Fourth Thursday of October, January and April.

PEDIATRIC SECTION OF THE NEW YORK ACADEMY OF MEDICINE

President: Dr. Stafford McLean, 17 East 71st St., New York.
Secretary: Dr. Frank Elmer Johnson, 300 West End Ave., New York.
Place: New York Academy of Medicine, 2 East 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

ROCHESTER PEDIATRIC SOCIETY

President: Dr. Paul W. Beaven, 26 S. Goodman St., Rochester, N. Y.
Secretary: Dr. Edwin R. Reynolds, 1620 St. Paul St., Rochester, N. Y.
Place: Arranged by Program Committee. Time: First Friday of each month from October to May.

THE PEDIATRIC SECTION OF THE ACADEMY OF MEDICINE OF CLEVELAND

Chairman: Dr. J. W. Epstein, 3912 Prospect Ave., Cleveland.
Secretary: Dr. Charles W. Burhans, 14805 Detroit Ave., Lakewood, O.
Place: 2009 Adelbert Road. Time: Four meetings, from September to May.

PEDIATRIC SECTION, ACADEMY OF MEDICINE, TORONTO

President: Dr. M. A. Cox, 34 St. Clair Ave. West, Toronto.
Secretary: Dr. F. R. Hassard, 1361 King St. West, Toronto.
Time: November 17, December 15, February 16 and March 15.

PHILADELPHIA PEDIATRIC SOCIETY

President: Dr. Edward L. Bauer, Jefferson Medical College, Philadelphia.
Secretary: Dr. John Porter Scott, 2040 Pine St., Philadelphia.
Place: College of Physicians, 19 S. 22nd St., Philadelphia. Time: Second Tuesday of each month from October to June, inclusive.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. W. D. Blue, 1024 Madison Ave., Memphis, Tenn.
Secretary: Dr. Gilbert J. Levy, 899 Madison Ave., Memphis, Tenn.
Place: Memphis General Hospital. Time: Second Tuesday of each month.

TEXAS PEDIATRIC SOCIETY

President: Dr. Edwin G. Schwarz, Medical Arts Bldg., Forth Worth.
Secretary-Treasurer: Dr. Ramsey Moore, Medical Arts Bldg., Dallas.
Place: San Antonio. Time: October, 1928.

RICHMOND PEDIATRIC SOCIETY

President: Dr. T. D. Jones, Medical Arts Bldg., Richmond, Va.
Secretary: Dr. W. Ambrose McGee, West End Medical Bldg., 2618 Grove Ave., Richmond, Va.
Place: Westmoreland Club, 601 E. Grace St., Richmond, Va.
Time: First Thursday of each month (other than during the summer).

VIRGINIA PEDIATRIC SOCIETY

President: Dr. Lawrence T. Royster, University, Va.
Secretary: Dr. William B. McIlwaine, Petersburg, Va.
Place: Danville, Va. Time: October 17, 1928.

NORTH PACIFIC PEDIATRIC SOCIETY

President: Dr. E. D. Carder, 736 Granville St., Vancouver, B. C.
Secretary and Treasurer: Dr. George A. Lamont, 736 Granville St., Vancouver, B. C.

SEATTLE PEDIATRIC SOCIETY

President: Dr. George B. McCulloch, Cobb Bldg., Seattle.
Secretary: Dr. C. L. Smith, Stimson Bldg., Seattle.
Place: College Club. Time: Third Friday of each month, at 7 p. m.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. A. B. Schwartz, 418 E. North Ave., Milwaukee.
Secretary: Dr. M. G. Peterman, 167 Seventeenth St., Milwaukee.
Place: Children's Hospital, Milwaukee. Time: Second Wednesday of each alternate month, beginning with February.

THE AMERICAN JOURNAL OF DISEASES OF CHILDREN is published by the American Medical Association as a means for the advancement of knowledge of the diseases of children and for the publication of scientific investigation in this field.

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